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Chapter 47

Issues and Challenges for Clinical Research in International Settings

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Chapter Outline

INTRODUCTION

Interest in public health is on the rise. Spreading beyond national boundaries, a shift in worldview to the "global village"[1] is bringing nations, races and ethnic groups together through economic activities, new media, cultural exchange, and easy travel. These unprecedented alliances are eroding physical and political barriers and opening up new opportunities for growth and change.[2]

Widespread infections like HIV, H5N1 virus, severe acute respiratory syndrome (SARS), and most recently H1N1, demonstrate the need to tackle health issues globally rather than locally.[3–6] In addition, initiatives like the Bill & Melinda Gates Foundation, United Nations Millennium Development Goals (MDG), the Global Fund and the United President's Emergency Fund for AIDS Relief (PEPFAR) have in different ways dramatically increased awareness of the state of global health. The poor state of health care delivery in many parts of the world and widening global health disparities increasingly are considered national security priority issues in many high resource countries.[7,8]

Tackling the global burden of disease will require improvement in accessibility to health care and the reversal of the disequilibrium in global health research investment that allots over 90% of the available funds to health problems affecting only 10% of the world population.[9] Furthermore, there is urgent need to develop innovative therapies and expand access to current therapies against diseases like the human immunodeficiency virus (HIV), multi-drug resistant tuberculosis (TB), and numerous emerging infectious diseases that pose major threats to the health of people in both resource-limited and resource-rich countries.[8] The discovery of these interventions and their accessibility will depend on the extension of clinical research studies to previously underrepresented populations across the world.[9,10]

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The conduct of such clinical studies at these international sites, especially in developing countries obviously are fraught with numerous challenges that require patience, an understanding of the local culture, and a firm determination to do the right thing. Some of these challenges include lack of well-developed Institutional Review Boards (IRBs), weak local research infrastructures, inadequate research workforce, language barriers, and poor socioeconomic status of the participants.

Furthermore, the health needs of developing countries are gradually extending beyond infectious disease following appreciable success in global economic development, the near eradication of polio, and better control of HIV and malaria.[11,12] The field of global health, which had in the past been almost synonymous with infectious disease, has evolved and now includes chronic non-communicable diseases (CNCD). Despite increases in the life expectancy and living standards in low and medium income countries, there is a widening health disparity with rapid increases in the prevalence of chronic non-communicable diseases like hypertension, diabetes, and cancer.[13] Since 2008, CNCD have been the predominant cause of death worldwide.[14] The World Health Organization (WHO) has predicted that 75% of all the deaths worldwide by 2020 will be due to CNCD with the majority of these occurring in developing countries.[13]

In order to alleviate the enormous global burden of communicable and non-communicable diseases, especially as it disproportionately impacts resource-limited countries, we must develop evidence-based interventions including better characterization of disease patterns and their associated socio-epidemiological factors. More efforts are needed to understand the pathogenesis of disease and the discovery of novel therapies targeted at neglected diseases that contribute to global heath disparities and inequities.[10]

HISTORICAL PERSPECTIVES

Many landmark discoveries having a significant impact on human health have emanated from clinical research conducted between investigators across geographical boundaries. Although some discoveries might be considered chance findings, many were achieved through transnational collaborations and meticulous execution. Epitomizing the role of international clinical scientist, in 1892 the exhaustive efforts of Sir Ronald Ross led him to the discovery that the mosquito bite is the channel through which malaria is passed to humans.[15] He later embarked on malaria control programs that spanned four continents with impact across and within various communities, including the construction of the Panama Canal.[16] Burkitt's lymphoma, first described by the English surgeon Denis Burkitt while working in Uganda,[17] was later associated with Epstein-Barr virus infection in the United Kingdom from tumor samples obtained from Africa.[18] The efficacy of oral rehydration therapy (ORT), which has completely revolutionized the treatment of diarrheal diseases, was established in studies done in Bangladesh.[19] The development of the yellow fever vaccine by Max Theiler also depended on findings extracted from different continents.[20] In 1968, Professor Familusi of the virology laboratory of the University of Ibadan in Nigeria identified Mokola virus as a cause of devastating aseptic meningitis.[21]

The full exploration of genetic information is believed to be the last frontier in medicine that will lead to the identification of the causes of disease, and their cures.[22] Building on this is another sterling example of the immense potential of cross-border collaboration, the Hap Map project.[23] It contains genetic information obtained from people of different ethnic and racial backgrounds across the world (Chinese, Japanese, Europeans, Nigerians, etc.). The publicly accessible genetic information provides a valuable resource for investigators that hopefully will lead to not only the identification of genes associated with specific diseases but their treatment response.

Overall, global collaboration and partnerships in research are necessary to combat both infectious and chronic non-communicable disease for the benefit of all, as demonstrated by past achievements with smallpox and polio.[24,25] The motivation to conduct clinical research in resource-limited countries—aside from being a moral imperative—is based on the overwhelming global desire to significantly reduce health disparities by developing evidence-based interventions that in the long-term serve strategic interests of resource rich countries.[7,26] In the post-genomic era, comparison data obtained from people of other races and ethnic backgrounds are helpful in validating findings among Caucasian populations on which most studies are currently performed.[27]

During the past decade, we have seen a shift of pharmaceutical companies moving many of their clinical trials offshore to developing countries because of lower cost, less-regulated IRBs, and an uneducated and uninformed populace whose rights often are ignored by investigators who often have an undeclared financial conflict of interest. Moreover, rapid subject accrual is seen as an opportunity to bring new drugs to market more quickly.[28] While this shift by pharmaceutical companies is most welcome, there are significant moral and ethical challenges that must be addressed promptly and adequately by the scientific community at a time when health disparities continue to widen and life expectancies in some low resource countries continue to fall.[29] Expanded global research should encompass equity, reduce health disparities, and promote societal benefits while advancing scientific discoveries. It must promote and adhere to basic ethical principles with respect to persons, beneficence, and justice.

Failure to adhere to ethical, moral and research principles has undermined society's trust in clinical research. These mistakes led to enacting policy to protect human subjects in research. However, the interpretations of established guidelines such as the Declaration of Helsinki developed by the World Medical Association may be interpreted differently according to the international setting;[29] this has enabled varying interpretations of ethical issues like injustice, coercion and exploitation.[30] For example, the capacity of participants to give "informed consent" often is questionable because most modern medical terms have no exact translations in local languages and the understanding of the causes and pathology of disease varies with culture and level of education.[31]

In clinical trial situations where most potential participants would otherwise have no access to treatment, their vulnerability and future access to the trial medication following study completion often raise ethical and moral concerns.[32] There is a long list of previous trials in developing countries that failed as a result of poor management and ethical and moral deficiencies; examples include prevention of vertical transmission of HIV in Africa[33] and the Trovan Trial by Pfizer in Nigeria.[34] Therefore, investigators interested in working across international borders especially in resource-limited settings need to be aware of the challenges and make necessary adjustments in the design and execution of their studies.

CHALLENGES

It is important that prior to beginning a study, collaborators identify possible pitfalls and develop solutions in advance to ensure a successful execution of the clinical research in a resource-limited setting. Many of the challenges are universal in these regions and include a lack of a skilled workforce, while others, such as cultural and religious beliefs and civil disorder, are region specific. In the proceeding subsections, we will briefly discuss some of the most common challenges and offer possible solutions.

Lack of a Skilled Workforce

The single most important challenge in conducting research in developing countries is the lack of a skilled workforce to support health care and clinical research.[35] While various factors have led to the systematic decline of higher education in most resource-poor countries, some major ones include inadequate leadership and investment in academic infrastructure, a general lack of awareness of scientific benefits by administrators and the public, and poor infrastructure development that leads to epileptic power supply.

Additionally, some contributing factors to the deteriorating quality of education and training are poor faculty development and the "brain drain" of academic staff. This human capital flight has particularly affected African countries, leaving an acute shortage of qualified academic staff within the higher education system to train the next generation of academic leaders. Specifically, well-trained health care professionals from African countries have flocked to more advanced, industrialized countries in North America and Europe.

According to data from the World Bank's publication World Development Report 2005, the per capita number of physicians (1/1,000) ranged from 3.58 to 3.97 in Sweden and Switzerland, but was 0.10 in Guinea and 0.02 in Rwanda, respectively.[36] This correlates with the per capita spending on health of $3,713 and $5,598, and $20 and $20, respectively, for the same countries. This huge disparity in health care spending is seen in the life expectancy data; and whereas spending has increased in developed countries, it remains low, especially in sub-Saharan Africa. The limited health-related spending is further worsened by corruption and poor management, which diverts more funds away from health.[37]

Worthy of mention is the 15–20-year downward trend in those applying to and graduating from medical schools in developing countries. This steady decline is problematic as there is no planned remediation in place to reverse this trend. Additionally, specific training in clinical research is usually not offered in postgraduate medical education.[38] Limited knowledge combined with deficient infrastructures has negatively impacted the quality of health services offered and the ability to conduct productive clinical research.

The deplorable state of health care delivery in most resource-limited countries is a direct result of poor remuneration and lack of incentive for faculty to be creative and innovative. Other factors outside university control, such as civil disorders, frequent and prolonged industrial strikes and lack of stable power supply, also impact productivity. These health care professionals either continue to underperform or they migrate to other countries in search of better career opportunities and improved job satisfaction.[35,39] Foreign-sponsored studies also can divert local health staff from direct clinical services that the community depends on to non-clinical positions with non-governmental organizations (NGOs) that mainly serve the purpose of the clinical research organization.[40] This so-called "brain waste" in which higher salaries and social status is used as a way to entice staff away from public service further depletes the pool of local health workers.

Local investigators complain too of a lack of recognition by foreign journals and funding agencies. The articles and grant applications they submit often are rejected as a result of "poor quality," which further decreases their job satisfaction.[41] Developing high-quality clinical research at international sites is attainable but requires significant investment of mentored training grants from funding agencies. By building local capacity, these investigators

will be given the opportunity for lead authorship on high-profile papers.

Deficient Infrastructures

Research infrastructure in most developing countries is poor. The better-equipped centers are concentrated in urban centers that often are physically and financially inaccessible to a majority of the population.[42] The health facilities and staff for clinical studies (primarily located in these urban centers) usually are inaccessible to the rural populations. The lack of basic resources such as transportation, sewage disposal, clean water and electricity make regular accessibility to these infrastructures almost impossible.

Inventory supplies from expensive replacement parts for laboratory equipment to cheap paper towels are all but non-existent and often require costly overseas shipping. Broken medical devices litter these resource-poor centers due to a lack of maintenance rendering them useless, resulting in wasted time and funds.

Meagerly Funded and Poorly Structured

The delivery of health to the general populace in most developed countries is seamless compared to the developing world, but this has occurred due to experience, capital investment, and opportunities to refine the process over time. For example, the National Health System (NHS) in the United Kingdom and the Servicio Sanitario Nazionale in Italy provide universal health coverage through public hospitals that is funded through tax policies. The systems in the Netherlands and Switzerland are based on compulsory insurance with built-in risk equalization to prevent setting premiums based on health status. Similarly, health care in France is offered by both private and public hospitals with a social security system that refunds most of the cost. The foundation of these systems is based on the revenue gained through higher taxes for high-income earners, making quality health care physically and financially accessible to virtually the entire population.

In contrast, most developing countries have meagerly funded and loosely organized health care systems.[13,43] Different levels of governments often fund the major portion of the health care services with the private and charitable organizations playing varying roles. Accessibility is impaired even further for women and children in many areas as a result of religious, cultural, and economic factors.[44] Furthermore, the coordination of service delivery through primary or secondary tiers is often poor and the referral system is not well developed, as most people do not have specific primary care providers.[45] These factors together impact the physical and financial accessibility to basic health care by the population.

Additionally, these fragmented health systems result in duplication of effort.[46,47] Foreign donors who often run non-overlapping, disease-specific, vertical programs without sharing resources and experiences fund a majority of the functional programs. Resources, both human and financial, also are wasted due to the lack of consolidation of clinical services and studies; instead separate but identical programs are run.[40,46,47]

Lack of Local Epidemiological Data

Basic epidemiological data are not available to researchers making it difficult to even know, let alone prioritize, health needs in developing countries.[48,49] Birth, death, and disease-specific registries are not maintained as government policies regarding these data, even when they do exist, are not enforced due to inadequate facilities and trained staff. Lack of these vital data critically impairs the capacity to project the exact extent of intervention that will be needed at a specific location and limits robust clinical research.[50,51]

Political Instability, Civil Disorders and Natural Disasters

Most developing countries have yet to attain the type of durable democracies of the west. As they live in a constant state of flux, continuous change to strata and forms of leadership impact field research.[52] At the local level, changes in the democratic and culture-based governance have a great impact on conducting clinical studies beyond granting permission and providing support. As most of these communities are tight-knit, the opinions of both spiritual and temporal authorities greatly impact the general population. Changes in such leadership following succession or political mechanisms invariably will impact studies, especially those requiring long-term follow-up. Frequent changes in governance also affect morale in terms of basic job security of local research staff; incessant turnover in management and its priorities can impair study continuity and undermine staff accrual of experience and job satisfaction.

Many of these societies too, are ravaged by internal conflict from civil uprisings to full-blown warfare. From Kashmir and Afghanistan in Asia, to Congo DR in Africa, to Colombia in South America and Chechnya in Russia, people live in varying degrees of danger. Such settings create numerous obstacles to producing good research, as the safety of both study participants and research staff may be compromised. There is concomitant change in the needs and priorities in such communities as the health needs will be largely first aid for physical injuries and the prevention of highly communicable diseases like cholera and typhoid fever.[53]

In cases of natural disasters, such as the Indian Ocean tsunami in 2004 and Haiti's earthquake in 2010, most of the surviving populations are displaced either temporarily or permanently.[54] With both wars and natural disasters also come the disruption of transportation and other infrastructures including hospitals, which are essential for the conduct of research.

Seasonal and Economic Migration

In many of the rapidly developing economies, for example in China, there is an unprecedented mass migration from rural to urban areas for economic reasons.[55] This migration negatively impacts studies that require long-term follow-up and also creates confounding factors that complicate data analysis. Also, in agricultural-based economies, people move from one region to another whenever poor climate conditions affect land cultivation.[56] In such cases, adults migrate temporarily in search of menial jobs. Similar to this group are pastoral nomads in sub-Saharan Africa, Mongolia, and other developing countries. There is limited availability of demographic and medical data on them and cultural barriers further complicates the research process as their willingness to talk to health care workers is limited.[56]

Physical Barriers

The distance between the developed north and developing south centers often precludes the opportunity for regular dialogue among scientists. Modern technology (phone, e-mail, and video conference) is only partially successful in creating a platform for conceptual exploration of the study and those modes of communication are not always as effective as in-person meetings. Travel expenses, including time lost, also increase overall study expense. The differences in time zones among study sites also may hamper regular communication leading to fragmented discussions via email.

Economic and Psychosocial Attributes of Study Participants

A majority of potential research participants in resource-poor countries share peculiar psychosocial and economic factors. Decisions to seek health care and to participate in clinical research are influenced by education-level, income, gender, religious, and traditional beliefs.[57–59] The overall perception of disease itself determines the health seeking behavior of individuals.[57,59] Such beliefs on the causes, treatments, and prognosis of illness vary greatly across international borders and even within communities and families.

Conversely, education or lack thereof has significant impact on one's type of occupation, level of income, quality of housing and access to medical care. More than that, it impacts one's health status and desire to seek treatment, and most importantly, determines one's capacity to be a part of the decision-making process involved in health care plans.[60] Many Western medical terms have no equivalent translation, making understanding of the pathology and prognosis of the disease difficult to interpret or explain.[61] In countries with prevalent inter-racial tensions, trust in both the health care system and the race of the health care provider can determine the choice of treatment (orthodox versus alternative) and health care facility.[62]

Ethical Issues

Ethical challenges to clinical research in developing countries often are controversial because of the peculiar socio-economical factors in these regions. The conceptual framework for clinical study design fits most perfectly into the socio-demographic characteristics of the predominant population in developed countries. However, several factors (income, cultural beliefs, level of education, etc.) may preclude the direct transfer of such framework of human research for minorities in the developed nations and for populations in developing countries. Several guidelines have been developed by a number of national and international organizations to guide the conduct of clinical research involving human subjects.[29,62–67] We will briefly highlight some salient aspects that are relevant to developing countries.

In the case of clinical trials in resource-poor settings since many would not otherwise have access to treatment, provision of study drugs may raise ethical issues of vulnerability, inducement and coercion, especially when tied together with payments to encourage participation.[68] Many of the international guidelines stipulate the universality of standard of care but there are legitimate questions about its practicality, especially in resource-poor settings.[29,69,70] For example, in the case of prevention of mother-to-child transmission of HIV, there are arguments on whether the accepted standard of care should be the one offered in the developed world or whether the local reality should be put in perspective.[68–71]

Making trial drugs "reasonably available" after the conclusion of the study to the community will add to the projected cost of the study and some have argued that this may actually discourage the execution of trials in resource-poor countries.[29,68,69,71] Culture and level of education also have impact on the understanding of disease and the concept of clinical studies and they raise questions about the capacity of many in developing countries to give informed consent.[31,61,68,69,71]

In cases of potentially fatal diseases like HIV/AIDS, the use of placebo control also has been challenged actively both on ethical and moral grounds.[33] First, many believe

that once an efficacious treatment already has been identified, there is no justification for the use of placebo controls; subsequent interventional studies should be done in comparison to the established standard regardless of local accessibility to the trial drug. Second, ethical requirements of Institutional Review Boards for human studies vary between countries.[72] In some cases in the developing world, they are in conflict as to whether their requirements should mirror what is available in the west or be tailored to the local reality. In some circumstances as well, nationalism and self-determination will influence the acceptance of foreign research proposals by local IRBs, transfer of samples and intellectual property rights.

The provision of ancillary care to the research participants and the community in general are controversial as it may act as inducement.[73] In summary, the conduct of clinical research studies in resource-poor countries is bound to raise several ethical and moral issues, especially where the current guidelines are not fully explicit in respect to prevailing socio-economic factors in these regions.

PROFFERED SOLUTIONS

Understand the Local Setting

The challenges that can be encountered during the execution of clinical research in international settings often vary with and within regions. In most cases, lessons learned from one region cannot always be applied to another region without significant modification. Investigators who intend to carry out studies in these settings thus need to educate themselves on region-specific details related to social structure, hierarchy, cultural beliefs, infrastructure, geography, weather patterns, and economic factors. Such understanding will help ensure a successful study as it can inform all aspects of the research, including selecting the best setting, designing sound research methods, using appropriate mechanisms for developing the sampling time frame, identifying the study population, and establishing controls and data collection methods.

For example, population responses may vary by cultural context. In a place like Costa Rica, health workers are revered with the population willing to participate in studies when approached. In contrast, rural residents in Kenya, Nigeria, and other parts of sub-Saharan Africa will not respond favorably to researchers (visitors) asking about their personal habits. Potential participants also are biased against public servants. Changing these attitudes will happen only when clinical studies are congruent with communities' perceived needs.[74] Studies on disease not considered a priority by the people may have difficulty in attracting and retaining participants. To find out the needs of a community, researchers must invest time in community engagement and education through information sessions first with community leaders and then with the community at large. Time should be allowed for a question-and-answer session where all ideas/concerns/attitudes are explored and societal benefits are highlighted.[75,76] Additionally, ethical issues should be addressed comprehensively while being sensitive to the local needs and cultures.[77,78]

Other issues should be considered carefully before embarking on studies in these developing countries. Of primary importance are the measures taken to protect the privacy of research participants, especially in studies involving stigmatized diseases such as HIV and acquired immunodeficiency syndrome (AIDS). Behaviors associated with these diseases such as homosexuality can carry risk of physical attack, and in some cases death. Repeated home visits by research workers also may bring to the attention of the whole community the health problems of study subjects, again leading to stigmatization.[79] It is advisable to ensure that the consent process is written at a 6th grade level at least for increased understanding,[80] and it should be as informational as possible going beyond simply translating into local languages. Tests should be conducted in order to assess the level of understanding of the consent at the commencement of the study and also regularly throughout the study duration.[80] Where surveys are involved, methods of maintaining quality control over the interviews should include the use of tape recorders, repeating questions, repeating visits, monitoring by supervisory staff and rapid review of completed questionnaires to identify errors and inconsistencies in subject responses. Ownership of the data and authorships also should be discussed ahead especially with local collaborators in order to avoid future conflicts.

A more sustainable solution to challenges posed by traditional methods of research where investigators retain all the authority—only seeking interaction with community when recruiting subjects and collecting data—is the adoption of a community-based or community-engaged participatory research model. This entails negotiations at all stages of the research, where both parties highlight concerns, discuss issues, and together reach consensus. This has the potential to benefit both the researchers and community because it facilitates easier enrollment of participants and data collection as the community sees themselves as equal partners in the process.[81] In fact, documenting the terms of the research process in the form of a memorandum of understanding or similar document may be helpful. Further, this model may involve open discussion of research results with stakeholders from the community, which can lead to improvements in the public health and well-being of the community. However, the dissemination of results entails risks and challenges that must be anticipated and well managed.

Develop and Enhance Local IRB Capacity

The rapid increase in the number of international clinical trials based in developing countries where research regulation is relatively weak calls for the development and expansion of capacity to conduct ethical research. Development of properly functioning IRBs can be a catalyst for increased research productivity at academic centers in developing countries while ensuring the protection of vulnerable human research subjects.[82] In response to the ethical lapses in a study that involved the use of the antibiotic Trovan that led to crippling injuries and death in Nigerian children, laws were enacted in an attempt to prevent future occurrences. Despite the recognition of the importance of a well-constituted ethics board in promoting research, funding support to meet the mandate often has lagged behind in many developing countries.

Train, Mentor and Closely Supervise

Initial training for research workers in developing countries needs to cover the basic principles of clinical research, design methods, and execution, including ethical oversight. This may be done better at centers in developing countries that offer similar settings rather than in a developed country. Efforts also should be made to develop independent local investigators and scientists through mentorship with training on how to write grants and protocol development.[83,84] At the initial stage, close supervision of the local study staff is required to ensure the ethical and judicious conduct of the study. Since in most instances many would lack the adequate clinical research skills and experience, technologies like video conferencing and VOIP (voice over internet protocol) can be utilized to provide frequent feedbacks on the progress of the study and also troubleshoot emerging issues.

Several approaches also can be employed to address the brain drain of health care and research workers.[85] These include provision of incentives and strong mentorship as well as grant, protocol, and article writing support. In addition, scientists from the north should be prepared to manage both the science and social aspects of the studies. They should not expect the same work habits, as planning, workloads, and sensitivity to deadlines and reporting vary with different cultures.

Develop Office of Sponsored Research

As the creation of functional IRBs expand there is a need for the creation of an office of sponsored research, charged with the responsibility of training all faculty, students and staff involved in research on current guidelines and changes in regulatory issues, while enhancing excellence and efficiency in project execution. Activities also should include establishing institutional research policies and provision of guidance on the conduct of clinical research and clinical trials and ensuring that all investigators, especially principal investigators, undergo required research training. Additional areas where the research enterprise may be enhanced include the handling of yearly declaration of conflict of interest statements, as well as development of management plans for situations where conflict of interest exists, and regulatory support for intellectual property rights.

Provide Ancillary Care

A statement in the commentary to the Council for International Organizations of Medical Sciences' Guideline 21 advises for the provision of health care to study participants beyond what is necessary for the clinical research.[63] This will improve the commitment of research participants and the community to the project with benefits to the overall health status.

Use of Technology for Effective Communication

Effective communication between the field and the international site is crucial and can make or break a study. Field updates on the project status should be frequent so that potential problems are identified and resolved quickly. The adoption of the Internet as a medium for real-time communication is important and provides significant support for projects. Other technologies like solar energy also have the potential to improve the execution and efficiency of clinical research projects through the provision of stable power supply, thereby lowering long-term costs.[86–88] It is essential to invest in the development of a computer and data management system with backup and maintenance plans due to the frequent power fluctuations and surges especially for studies conducted in developing country settings where energy poverty is a problem.[89]

Have Long-term Plans

Most studies in developing countries often are short in duration, goals, and scope. Lack of continuity usually leads to wasted resources and may negatively impact the community's willingness to take part in future studies. Even for studies that are designed initially to be short in duration such as an interventional study, efforts should be made to maintain some form of contact with the local staff and community for continuity.

Integrate with Existing Infrastructure

Despite the obvious fact that in many regions of the developing world the health infrastructures are in

deplorable conditions with non-functioning health systems, it is advised that efforts be made to integrate new studies into whatever system is available locally. Such integration will prevent research workers from completely abandoning their primary duty of offering care to the general population and also further strengthen the local health system.

Prepare Data Safety and Monitoring Plan for Adverse Events

There is need to put in place contingency plans to address adverse events before they occur. A standard operating procedure (SOP) to deal with such eventualities should be devised and training should be offered upon initiation of the research study. Another essential aspect of preparation for clinical research studies that is often lacking is the development of a data safety and monitoring plan (DSMP). Ideally, this should be developed prior to initiation of any clinical trial to define activities that need monitoring such as informed consent, integrity of data collection, processing, and review of plans for adverse events handling, protocol deviation and violations. In clinical trials where death or morbidity are potential end points, the DSMP should involve creation of a data safety monitoring board (DSMB) to make timely decisions about the need to stop a study prematurely or to modify informed consent forms if necessary to deal with emerging risks.

CONCLUSION

Improvements in global access and quality of health care are going to be dependent on the discoveries of socio-epidemiological risk factors for diseases, innovative therapies, and their equitable distribution. Unfortunately, third world countries that have grave health concerns are critically deficient in the capacity to independently execute these. Among the innumerable challenges they face are deficient health systems, lack of a skilled workforce, as well as economic and psychosocial factors of potential participants. Addressing these issues will impact greatly the success of clinical studies.

Researchers with interests in conducting clinical studies in resource-limited countries first need to understand the people they will be studying. The community's perception of disease and priority of needs, in addition to trust in the health care system and research workers, all together determine the success of recruitment and retention of participants. It is necessary to develop partnerships with communities as a means to engage the people and leaders in shared planning and execution of studies, in order to create mutual trust and respect and a sense of co-ownership of research projects.

Training of local research staff must be comprehensive in addition to offering continuing guidance and mentorship. Utilization of the Internet and computerization of as many sections of the study as possible will improve communication, accuracy, and efficiency. Additional technologies to be utilized need to be durable and well suited for the local settings, and plans to sustain the program should be factored in at the initial stage. Efforts should be made to avoid fragmentation through the integration of studies into the existing health system. Sharing experiences with study groups working in similar settings may further improve efficiency and reveal initially unanticipated adverse events that need to be tackled preemptively.

Conducting successful cross-border clinical research will require more than just science. Knowledge of sociology, anthropology, and site-specific human resource management is vital. There should be willingness to be open and flexible with readiness to adjust to differing research habits, public policy concerns, and institutional arrangements. Finally, the benefits of conducting clinical trials on international settings eventually may be universal. However, it requires a lot of preparation and willingness to abide by established ethical and moral guidelines with local relevance.

SUMMARY QUESTIONS

1. Which of the following are recognized challenges to the conduct of reliable clinical trials in developing country settings?
   - **a.** Lack of resources and infrastructure for research
   - **b.** Poor data collection methods
   - **c.** Questionable ethical standards and poor subject protection
   - **d.** All of the above
2. Use of placebos in clinical trials is justifiable under the following conditions
   - **a.** When there are approved and effective treatments for the condition
   - **b.** If there is no disagreement about whether standard treatment is better than placebo
   - **c.** When the additional risk posed by the use of placebo is minor and withholding the current standard therapy would not lead to serious or permanent harm
   - **d.** If the study is being conducted in an international setting where standard therapy is unavailable
3. Which of the following are true regarding informed consent for studies in international settings?
   - **a.** Societal benefit trumps individual risks in clinical research
   - **b.** Risk-to-benefit ratio should always be in favor of the community
   - **c.** The epidemic potential of a disease may shift risk–benefit ratio in favor of the community

d. Cultural values and norms can influence informed consent process

4. Which of the following are important for successful conduct of clinical trials in international settings?
   a. Knowledge of cultural beliefs and seasonal patterns
   b. Planning for alternative power supply
   c. Developing effective communication and data storage systems
   d. Community engagement and partnership
   e. All of the above
5. Which of the following is the most important benefit of international clinical trials?
   a. Contribution to improvement in global diplomacy
   b. Reduction of global health disparities
   c. Opportunity to study new drugs in a population with less likelihood of drug/drug interactions
   d. None of the above

REFERENCES

1. Yach D, Bettcher D. The globalization of public health, I: Threats and opportunities. *Am J Public Health* 1998;**88**:734−8.
2. Drager N, Beaglehole R. Globalization: changing the public health landscape. *Bull World Health Organ* 2004;**79**:875−81.
3. Quinn TC. Global burden of the HIV pandemic. *Lancet* 1996;**348**:99−106.
4. Li KS, Guan Y, Wang J, Smith GJ, Xu KM, Duan L, et al. *Nature* 2004;**430**:209−13.
5. Zhao Z, Zhang F, Xu M, Huang K, Zhong W, Cai W, et al. *J Med Microbiol* 2003;**52**:715−20.
6. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *J Clin Virol* 2009;**360**:2605−15.
7. Fox DM, Kassalow JS. Making health a priority of US foreign policy. *Am J Public Health* 2001;**91**:1554−6.
8. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. *Nature* 2008;**451**:990−3.
9. Global Forum for Health Research. 10/90 Report on Health Research, 2002. Online. Accessed February 23, 2011.
10. Laxminarayan R, Mills AJ, Breman JG, Measham AR, Alleyne G, Cleason M, et al. Advancement of global health: key messages from the disease control priorities project. *Lancet* 2006;**367**:1193−208.
11. UNAIDS. AIDS Epidemic Update 2009. Online, <http://www.unaids.org/en/dataanalysis/epidemiology/2009aidsepidemicupdate/>. Accessed February 23, 2011.
12. Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO. Changes in malaria indices between 1999 and 2007 in the Gambia: a retrospective analysis. *Lancet* 2008;**372**:1545−54.
13. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global burden of diseases and risk factors. *Lancet* 2006;**367**:1747−57.
14. World Health Organization. *World Health Statistics*. Online at, <http://www.who.int/whosis/whostat/2008/en/index.html>; 2008. Accessed February 23, 2011.
15. Chernin E. Sir Ronald Ross, malaria, and the rewards of research. *Med Hist* 1988;**32**:119−41.
16. Marshall L. The Story of the Panama Canal. *L.T. Myers*; 1913: pp. 1−358.
17. Burkitt DP. A sarcoma involving the jaws in African children. *Br J of Surg* 1958;**46**:218−23.
18. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964;**1**:702−3.
19. Ruxin JN. Magic bullet: the history of oral rehydration therapy. *Med Hist* 1994;**38**:363−7.
20. Theiler M, Sellards AW. Immunological relationship of yellow fever as it occurs in West Africa and South America. *Ann Trop Med* 1928;**22**:449−60.
21. Familusi JB, Moore DL. Isolation of a rabies related virus from the cerebrospinal fluid of a child with "aseptic meningitis." *Afr J Med Sci* 1972;**3**:93−6.
22. Venter JC. The sequence of the human genome. *Science* 2001;**291**:1304−51.
23. The International HapMap Consortium. The International HapMap Project. *Nature* 2003;**426**:789−96.
24. World Health Organization. Smallpox eradication in 1975. *WHO Chron* 1976;**30**:152−7.
25. World Health Organization. Vaccine and polio immunization in the pre-eradication era: WHO position paper—recommendations. *Vaccine* 2010;**28**:6943−4.
26. Garrett L. *The Coming Plague: Newly Emerging Diseases in A World Out of Balance*. Penguin; 1995.
27. Marchini J, Cardon LR, Phillips MS, Donnelly P. The effects of human population structure on large genetic association studies. *Nat Genet* 2004;**36**:512−7.
28. Shuchman M. Commercializing clinical trials—risks and benefits of the CRO book. *N Engl J Med* 2007;**357**:1365−8.
29. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Online at, <www.hpci.ch/files/documents/guidelines/hh_gl_helsinki.pdf>. Accessed February 23, 2011.
30. Johnatty RN. Meeting report: clinical trials in developing countries: discussions at the 9th International Symposium on Long Term Clinical Trials, London, UK, June 19−20, 2000. *Curr Control Trials Cardiovasc Med* 2000;**1**:55−8.
31. Fitzgerald DW, Marotte C, Verdier RI, Johnson Jr WD, Pape JW. Comprehension during informed consent in a less-developed country. *Lancet* 2002;**360**:1301−2.
32. Brody BA. Ethical issues in clinical trials in developing countries. *Statist Med* 2002;**21**:2853−8.
33. Perinatal HIV. Intervention Research in Developing Countries Workshop Participants. Science, ethics and the future of research into maternal infant transmission of HIV-1. *Lancet* 1999; **353**:832−5.
34. Lenzer J. Secret report surfaces showing that Pfizer was at fault in Nigerian drug tests. *BMJ* 2006;**332**:1233.
35. Naicker S, Plange-Rhule J, Tutt RC, Eastwood JB. Shortage of healthcare workers in developing countries—Africa. *Eth Dis* 2009;**19**(Suppl.):S16−64.
36. *World Bank. World Development Report*. Online at, <http://web.worldbank.org/WBSITE/EXTERNAL/EXTDEC/EXTRESEARCH/EXTWDRS/EXTWDR2005/0, contentMDK:20259914~menuPK:477673~pagePK:64167689~piPK:64167673~theSitePK:477665,00.html>; 2005. Accessed February 23, 2011.
37. Sharma SP. Politics and corruption mar healthcare in Nepal. *Lancet* 2010;**375**:2063−4.

38. Lansang MA, Rodolfo D. Building capacity in health research in the developing world. *WHO Bulletin* 2004;**82**:764−70.
39. Editorial. Medical migration and inequity of healthcare. *Lancet* 2000;**356**:177.
40. Pfeiffer J. International NGOs and primary healthcare in Mozambique: the need for a new model of collaboration. *Soc Sci Med* 2003;**56**:725−38.
41. Costello A, Zumla A. Moving to research partnerships in developing countries. *BMJ* 2000;**321**:827−9.
42. Zaidi SA. The urban bias in health facilities in Pakistan. *Soc Sci Med* 1985;**20**:473−82.
43. Lu C, Schneider MT, Gubbins P, Leach-Kemon K, Jamison D, Murray CJL. (2010). Public financing of health in developing countries: a cross-national systematic analysis. *Lancet* 2010;**375**:1375−87.
44. Lawn JE, Lee AC, Kinney M, Sibley L, Carlo WA, Paul VK, et al. Two million intrapartum-related stillbirths and neonatal deaths: where, why, and what can be done? *Int J Gynaecol Obstet* 2009;**107**:S5−18. S19.
45. Rohde J, Cousens S, Chopra M, Tangcharoensathien V, Black R, Bhutta ZA, et al. 30 Years after Alma-Ata: has primary healthcare worked in countries? *Lancet* 2008;**972**:950−61.
46. England R. The dangers of disease-specific programs for developing countries. *BMJ* 2007;**335**:565.
47. Biesma RG, Brugha R, Harmer A, Walsh A, Spicer N, Walt G. The effects of global health initiatives on country health systems: a review of the evidence of HIV/AIDS control. *Health Policy Plan* 2009;**24**:239−52.
48. Ramanakumar AV. Need for epidemiological evidence from developing world to know the cancer-related risk factors. *J Cancer Res Ther* 2007;**3**:29−33.
49. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic disease: overcoming impediments to prevention and control. *JAMA* 2004;**291**:2616−22.
50. Gonzalez-Pier E, Gutierrez-Delgado C, Stevens G, Barraza-Llorens M, Porras-Condey R, Carvalho N, et al. Priority setting for health interventions in Mexico's system of social protection in health. *Lancet* 2006;**368**:1608−18.
51. Timaeus I, Harpham T, Price M, Gilson L. Health surveys in developing countries: the objectives and design of an internation program. *Soc Sci Med* 1988;**27**:359−68.
52. Rifkin SB. Lessons from community participation in health programmes. *Health Policy Plan* 1986;**1**:240−9.
53. Sidel VW, Levy BS. The health impact of war. *Int J Inj Contr Saf Promot* 2008;**15**:189−95.
54. Waring SC, Brown BJ. The threat of communicable diseases following natural disasters: a public health response. *Disaster Manag Response* 2005;**3**:41−7.
55. Murphy R. *How Migrant Labor is Changing Rural China*. United Kingdom: Cambridge University Press; 2002.
56. Mohamed A, Velema JP. Where health care has no access: the nomadic populations of sub-Saharan Africa. *Trop Med Int Health* 1999;**4**:695−707.
57. Rasco DW, Xie Y, Yan J, Sayne JR, Skinner CS, Dowell JE, et al. The impact of consenter characteristics and experience on patient interest in clinical research. *Oncologist* 2009;**14**:468−75.
58. Pachter LM. Culture and clinical care: folk illness beliefs and behaviors and their implications for healthcare delivery. *JAMA* 1994;**271**:690−4.
59. Sharp K, Ross CE, Cockerham WC. Symptoms, beliefs and the use of physician services among the disadvantaged. *J Health Soc Behav* 1983;**24**:255−63.
60. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment? *BMJ* 1999;**319**:780−2.
61. Sechrest L, Fay TL, Hafeex Zaidi SM. Problems of translations in cross-cultural research. *J Cross-Cultural Psych* 1972;**3**:41−56.
62. Saha S, Komaromy M, Koepsell TD, Bindman AB. Patient-physician racial concordance and the percieved quality and use of healthcare. *Arch Intern Med* 1999;**159**:997−1004.
63. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Guideline 21, 2002. Online at, <http://whqlibdoc.who.int/emro/2004/9290213639_annex2.pdf>. Accessed February 24, 2011.
64. World Health Organization. Handbook for Good Clinical Research Practice (GCP). Guidance for Implementation. Online at, <http://whqlibdoc.who.int/publications/2005/924159392X_eng.pdf>. Accessed February 24, 2011.
65. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Online at, <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>; 1979. Accessed February 24, 2011.
66. National Institute of Health. *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health*. Online at, <http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf>; 2001. Accessed February 24, 2011.
67. Nuremberg Code. Directives for Human Experimentation. Online, http://ohsr.od.nih.gov/guidelines/nuremberg.html. Accessed February 24, 2011.
68. Barry M. Ethical considerations of human investigation in developing countries. *N Eng J Med* 1988;**319**:1083−6.
69. Sharpiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. *N Eng J Med* 2001;**345**:139−42.
70. Wendler D, Emmanuel EJ, Lie RK. The standard of care debate: can research in developing countries be both ethical and responsive to those countries' health needs? *Am J Public Health* 2004;**94**:923−8.
71. Benatar SR. A new look at international research ethics. *BMJ* 2000;**321**:824−6.
72. McWilliams R, Hoover-Fong J, Hamosh A, Beck S, Beaty T, Cutting G. Problematic variation in local institutional review of a multicenter genetic epidemiology study. *JAMA* 2003;**290**:360−6.
73. Belsky L, Richardson HS. Medical researchers' ancillary clinical care responsibilities. *BMJ* 2004;**326**:494−6.
74. Cornwall A, Jewkes R. What is participatory research? *Soc Sci Med* 1995;**41**:1667−76.
75. Chitambo BR, Smith JE, Ehlers VJ. Strategies for community participation in developing countries. *Curationis* 2002;**25**:76−83.
76. Laung MW, Yen IH, Minkler M. Community based participatory research: a promising approach for increasing epidemiology's relevance in the 21st century. *Int J Epidemiol* 2004;**33**:499−506.
77. London L. Ethical oversight of public health research: can rules and IRBs make a difference in developing countries? *Am J Public Health* 2002;**92**:1079−84.
78. McIntosh S, Sierra E, Dozier A, Diaz S, Quinones Z, Primack A, et al. Ethical review issues in collaborative research between US and low-middle income country partners: a case example. *Bioethics* 2008;**22**:414−22.

79. Hotez P, Ottesen E, Fenwick A, Molyneux D. The neglected tropical diseases: the ancient afflictions of stigma and poverty and the prospects for their control and elimination. *Adv Exp Med Biol* 2006;**582**:23−33.
80. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research. *JAMA* 2004;**292**:1593−601.
81. Ross LF, Loup A, Nelson RM, Botkin JR, Kost R, Smith Jr GR, et al. Human subjects protections in community-engaged research: a research ethics framework. *J Empir Res Hum Res Ethics* 2010;**5**:5−17.
82. Falusi AG, Olopade OI, Olopade CO. Establishment of a standing ethics/institutional review board in a nigerian university: a blueprint for developing countries. *J Empir Res Hum Res Ethics* 2007; **2**:21−30.
83. Lasang MA, Dennis R. Building capacity in health research in the developing world. *Bull World Organ* 2004;**82**:64−770.
84. Narasimhan V, Brown H, Pablos-Mendez A, Adams O, Dussault G, Elzinga G, et al. Responding to the Global Human Resources Crisis. *Lancet* 2004;**363**:469−72.
85. Stiwell B, Diallo K, Zurn P, Vujicic M, Adams O, Dal Poz M. Migration of healthcare workers from developing countries: strategic approaches to its management. *Bull World Health Organ* 2004;**82**:595−600.
86. Avilles W, Ortega O, Kuan G, Coloma J, Harris E. Integration of information technologies in clinical studies in Nicaragua. *PLoS Med* 2007;**4**:e291.
87. Gotch F, Gilmour J. Science, medicine and research in the developing world: a perspective. *Nat Immunol* 2007;**8**:1273−6.
88. Hueck CC, Deom A. Healthcare in the developing world: need for approproate laboratory technology. *Clin Chem* 1991;**37**:490−6.
89. Lee PD. The role of appropriate medical technology procurement and user maintenance instructions in developing countries. *J Clin Eng* 1995;**20**:407−13.