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Original paper

# Ethical oversight of multinational collaborative research: lessons from Africa for building capacity and for policy

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*Researchers and others involved in the research enterprise from 12 African countries met with those working in ethics and oversight in the United States as part of an effort to develop research ethics capacity. Drawing on a wealth of experience among participants, discussions at the meeting revealed five categories of issues that warrant careful attention by those engaged in similar efforts as well as international policymakers and those charged with oversight of research. (1) Principal investigators should build 'true research teams' where members of the team are meaningfully involved in decisions regarding the protocol and its implementation. (2)There should be explicit discussion about the 'standard of care' at the outset of project planning that includes clarification of the terminology that is being used. (3) While internationally collaborative research may involve populations that have inherent vulnerabilities, it is important to recognize the limitations of host country solutions (such as elaborated consent processes) and look for means to negotiate appropriate protections for those willing to participate. (4) In conducting research involving biological materials it would be prudent to develop material transfer agreements at the outset of the study to clarify expectations and to minimize the likelihood of harm. (5) Those engaged in internationally collaborative research need to be alert to the potential conflicts of interests of host country ethics committees during the approval process and to take measures to manage them if they indeed exist.*

## Introduction

To address serious ethical concerns about internationally collaborative research, considerable efforts are being taken to develop research ethics capacity across the globe. This includes training researchers and those charged with ethical oversight in host countries [1,2]. Researchers and others involved in the research enterprise from 12 African countries recently met with those working in ethics and oversight in the United States as part of a capacity building effort. Drawing on a wealth of experience among participants, discussions at the meeting revealed five categories of issues that warrant careful attention by those engaged in similar efforts as well as international policymakers and those charged with oversight of research. In this report, we summarize these important issues.

## Background

There is now a considerable volume of multinational research conducted in many African countries with collaborators from other parts of the world. While this research is ideally aimed at addressing some of the enormous burdens of disease that can be exacerbated by poverty, a variety of concerns have been raised about the ethics of this research in medical journals, the popular press, and popular culture. For example, publications in professional journals have wrestled with the vexing debate about the ethical issues associated with a series of trials that were aimed at decreasing the vertical transmission of HIV from mother to child that employed placebo arms [3]. Subsequently, the *Washington Post* published a series of articles describing the ethical issues that

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arose in research involving the use of an antibiotic to treat meningitis in children [4]. Further, the film version of John le Carré's novel, *The Constant Gardener*, released in 2005, suggested an array of issues allegedly associated with research, especially conflicts of interest among sponsors [5].

Such concerns have not gone unnoticed by those in positions of ethical oversight of research. Indeed some of these discussions were associated with revisions of the Declaration of Helsinki and the CIOMS International Ethical Guidelines as well as reports by prominent groups and governmental commissions, such as the Nuffield Council on Bioethics and the US National Bioethics Advisory Commission [6,7]. While a variety of measures have been suggested for ensuring that multinational collaborative research is conducted in an ethical fashion, one approach that has met with substantial support is developing research ethics capacity. To be effective, such training must be sensitive to the types of cases and issues faced locally. In addition, such cases and issues can be informative for all of those involved in multinational collaborative research.

Through our capacity building partnership, five categories of issues related to the ethics of international collaborative research have emerged that warrant careful attention by those engaged in such research: (1) the roles of investigators; (2) confusion regarding standards of care; (3) problematic aspects of labeling participants as vulnerable; (4) troubles related to biological materials; and (5) powerful manifestations of conflicts of interest. Each will be discussed in turn.

## Roles of investigators

The role of the principal investigators (PIs) and other investigators in the host and sponsoring countries can be unclear. Although in all research PIs have central moral responsibility for the scientific and ethical aspects of research, in international collaborative research where the PI is from a sponsoring country, host country investigators who may hold the local title of 'PI', may sense a lack of real control over the research. As such, they may not feel empowered to modify a protocol, provided by a sponsoring country PI, to protect the rights and interests of the participants. In reality, each research project has only one PI, independent of geographical location, regardless of the titles applied to other investigators. Nevertheless, this hierarchical structure may make it difficult for investigators working in host countries to insist upon modifications of protocols and procedures that will best protect participants, yet the obligation to protect participants is non-negotiable for all members of the research team. Therefore, efforts should focus on having local and host country investigators, regardless of title, take responsibility for moral and scientific aspects of protocols. This could be effectuated by building 'true research teams' where members of the team are meaningfully involved in decisions regarding the protocol and its implementation. Inevitably each team should have a leader, and the PI's role is best considered one of leadership.

## Standards of care

There is substantial confusion about 'standards of care' in the research setting that leads to considerable discord and uncertainty for those engaged in multinational collaborative research. Part of this confusion is reflected in the use of different terms in different seminal documents, such as 'best proven therapeutic method', 'established effective treatment', etc. While the term 'standard of care' derives from the law and indicates typical practices in a given situation, some have argued that in the research setting, the highest attainable or highest sustainable care must be provided regardless of what is typically done locally [8]. Such arguments leave unresolved what to do in situations when there is a lack of consensus even among health care professionals about what such care might optimally entail. In addition, such arguments may suggest some confounding of the goals of either (a) research and clinical care or (b) conducting research and reducing global health inequities. Moreover, even if such an obligation that exceeds what is typically available is assumed, the practical reality is that many sponsors may not have adequate resources to address such needs, obviating the possibility of some research. Given the amount of confusion and the high stakes involved, there should be explicit discussion about this issue at the outset of project planning that includes clarification of the terminology that is being used in these discussions. Community engagement with relevant stakeholders may also be useful.

## Vulnerability

The label of 'vulnerability' may be harmful as well as helpful if the provisions typically used to protect the 'vulnerable' are employed automatically [9]. For example, in trials designed to decrease the perinatal transmission of HIV infection, using the US regulatory approach both the pregnant woman and the fetus would be considered vulnerable, invoking special protections such as the requirement for paternal as well as maternal consent to participate [10]. However, in some settings in Africa a requirement for paternal consent may create harm since some fathers may react to such a situation by abusing or neglecting the HIV-infected pregnant woman. Similarly, if paternal consent is obtained for continuing participation of the child in research following the death of the mother the child may experience harms including not having school fees paid or abandonment. In other cases, such as research involving orphans and vulner-

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able children, it may be impossible to identify legally authorized representatives to provide consent on behalf of the participants. Given such situations, it is important to recognize the limitations of host country solutions (such as elaborated consent processes) to such desperate situations and look for means to negotiate appropriate protections for those willing to participate in such critically needed research.

## Biological materials

Collaborative research involving biological materials can be complicated by the disposition of these materials following the research [11]. Although such research in any setting can raise important issues related to consent, ownership, and the social harms related to aggregated results, the latter may be of special salience in multinational collaborative research. In addition, there may be cultural practices regarding particular biological tissues, such as blood or the placenta that need to be recognized [12]. Accordingly, in conducting research involving biological materials it would be prudent to develop material transfer agreements at the outset of the study to clarify expectations and to minimize the likelihood of harm. To make this task easier, it would be useful to have a content analysis of successful agreements so that model features and best practices might be identified.

## Conflicts of interest

Host country research ethics committee (or institutional review board) members can face difficult challenges related to conflicts of interest. It is obvious to members of host country ethics committees that if they disapprove research, research and the funds associated with it will not transfer to their institutions and communities, putting enormous pressure on them to approve the research. This may affect not only the 'institutional' members of the committees, but also the community members. While a solution to this issue is not readily apparent, an important first step is to explicitly acknowledge these conflicts during the review. It may also be worthwhile for sponsoring country ethics committees to be made aware of these potential conflicts during their review and to take measures to manage them if they indeed exist.

## Concluding comments

The process of building capacity in research ethics can make evident relevant issues for global research ethics. While we describe some of these issues and offer some preliminary suggestions for dealing with them, future work should assess their effectiveness and applicability. Finally, systematic descriptions of the types of issues encountered in this sort of research is clearly needed to help develop means of protecting the rights and interests of those participating in multinational collaborative research.

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