



Module 5

Ethical Issues in International Collaborative Health Research

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1.0 INTRODUCTION

International collaborative research in the past decade has led to an increase in partnerships that bring together researchers from developed and developing countries. Such collaborations pose complex challenges largely due to inequities in health care systems within and between countries and socioeconomic factors prevailing in different countries. Concerns have been expressed about the ethics and practical challenges of health research in developing countries, and this module covers some of the topical issues surrounding international collaborative research. The module ends with a case study that captures some of the pertinent issues, with a few questions to guide discussion.

OBJECTIVE OF THE MODULE

The objective of this module is to highlight some of the ethical and practical issues that need to be critically considered before engaging in international collaborative health research, especially when both developing and developed countries are involved. It is hoped that the module will enhance the ability of researchers to deal with pertinent issues surrounding international collaborative research.

The module will cover the following issues:

- The need for health research
- North-South and South-South collaboration
- Some critical issues to be agreed on upfront
 - Roles and responsibilities of the stakeholders involved
 - Ethical approval and regulatory authorities
 - Standard of care: during and post-study (if applicable)
 - Capacity building

- Sharing and ownership of samples: during and post-study
- Data sharing policy: during and post-study
- Intellectual property rights
- Information dissemination and authorship

3.0 THE NEED FOR HEALTH RESEARCH

Although globally there have been significant advances in the medical field, the disease burden of developing countries is still very high. The situation has been worsened by socioeconomic challenges that have led to inadequate and/or poor health delivery systems. In terms of health research, it has been reported that only 10% of the global research funds are spent on health research and development (R&D) aimed at addressing health problems that affect 90% of the global population. It is in light of these challenges that efforts to address the plight of developing countries have been intensified.

Various players such as the United Nations, the Global Health for Health Research, the World Health Organization and the private sector have scaled up their efforts to improve the health of mankind. Philanthropic and non-governmental organizations have been playing a major role in various health-related areas where they complement efforts by governments to improve the health of their citizens. The major diseases that affect developing countries include TB, malaria, HIV/AIDS, respiratory infections and diarrhea. In contrast, lifestyle health conditions such as obesity, heart diseases, stroke, type 2 diabetes, cancer and depression are the major challenge for developed countries.

The need for health research is also due to the emergence of new diseases. Examples of such new diseases are HIV/AIDS, Ebola, Severe Acute Respiratory Syndrome (SARS), Multi-Drug Resistant Tuberculosis (MDRTB) and Extreme Drug Resistant Tuberculosis (XDR TB). In addition, some diseases the incidence rate of which had significantly declined are re-emerging; examples include dengue hemorrhagic fever caused by flaviruses, plague caused by *Yersinia pestis* and cholera caused by *Vibrio cholerae*. Further, emergence of drug resistant strains of pathogens is also problematic as it renders previously efficacious tools to be ineffective.

4.0 NORTH-SOUTH AND SOUTH-SOUTH COLLABORATION

Whereas in the past most research used to be localized at institutions or in particular countries, the trend recently has been the formation of collaborative research projects that involve researchers from different institutions and in most cases from different countries. North-South collaborative research usually involves formation of consortia made up research institutions in developed and developing countries. In most north-south international collaborative research projects, institutions in developed countries are the recipients of research grants, with the principal investigators (PIs) based at such institutions and researchers from collaborating institutions being co-PIs. Recently, efforts to promote south-south collaboration in research have intensified. South-south collaborations aim to take advantage of existing expertise and facilities in the regions, especially where countries have more or less similar health needs.

The need for collaborative efforts in health research could be attributed to a combination of many factors that include the following;

- Need to share expertise in various fields of specialization
- Need for large sample sizes which could take prohibitively long periods of time to achieve if individual institutions were to collect the samples alone; examples are epidemiological studies and randomized controlled trials.
- Inadequacy or lack of high-tech laboratories at some institutions, especially in developing countries
- Poor state or lack of appropriate infrastructure, especially in developing countries
- Low prevalence of diseases of interests in some countries, especially developed countries, which could have practical implications on recruitment of research participants and sample collection

5.0 SOME CRITICAL ISSUES TO BE AGREED UPON UPFRONT

It is critical for players involved in international collaborative research to agree on pertinent issues before the research commences. Dealing with relevant issues upfront helps to minimize potential disagreements that could jeopardize the collaboration and conduction of the research. Assumptions and uncertainties need to be tackled as early as possible and all stakeholders need to be consulted as much as possible.

5.1 Roles and responsibilities of the stakeholders involved

The roles of the PI and co-PIs should be clearly spelt out. A governance structure for the whole collaborative group should be developed and agreed upon. It is also important to put in place decision making processes for administrative as well as for technical issues. Similarly, the roles of institutions taking part in the collaborative research should be clarified. Budgetary implications of the roles of the various players need to be transparently dealt with. The details of these issues could be in such documents as constitution, memorandum of understanding (MOU) and contracts.

5.1.1 Some ethical and practical issues

- If researchers are regarded as PIs or co-PIs, then their roles and responsibilities in collaborative research should reflect that they are PIs. Local PIs should therefore take responsibilities pertaining to the collaborative research, and the protection of the welfare of local research participants is primarily their responsibility since they are the ones who interact with the participants. The fact that samples may have been shipped to some foreign country for analysis does not lessen the responsibility of the local PIs. However, as a team of researchers, all PIs are responsible for the overall welfare of research participants and their communities.
- As PIs, it means that the researchers should have access to data collected in the collaborative research; otherwise the local PIs could be viewed as mere 'sample collectors'
- The PIs of a collaborative research project should plan for and implement community consultation activities if deemed critical; it is not up to the local collaborating PIs to do it or not. Although the local PIs would be the ones to be in the forefront, the whole collaborative project is responsible for ensuring appropriate engagement with the communities from which participants are drawn.
- Researchers and their institutions should strive to always uphold the ethical principles of beneficence and justice by ensuring that the research conducted in their localities is relevant to the health-related needs of the local communities. Thus local researchers and their institutions should not facilitate entry of foreign researchers, from developing or developed countries, who disappear as soon as they have collected enough samples for their studies and never return to feed back results to the participating communities.
- Institutions have the responsibility to ensure that their employees conduct research ethically and legally. Institutional policies should guide researchers as they enter into collaborative research.

- All financial responsibilities of the sponsor of collaborative research should be clear to all the stakeholders; it should not be assumed that the sponsor will be responsible for certain aspects of the research without prior discussions and agreements. This is especially critical if there are some post-study activities that require funds.

5.2 Ethical approval and other regulatory requirements

Ethical approval for collaborative research should be obtained from each of the local Ethics Review Committees that are mandated to review protocols for the participating institutions. An ethical approval obtained in one country by researchers based at a particular institution is not valid for research activities to be carried out by collaborating researchers based at another institution in a different country. Depending on the type of research, it may be necessary to meet certain local regulatory requirements. For instance, if it is multi-centre clinical trials, requirements of local medical regulatory authorities have to be met. Another example is regulatory requirements for exportation of samples to other countries.

5.2.1 Some ethical and practical issues

It is the responsibility of all the PIs (local or foreign) to ensure that approval is obtained and that any other regulatory requirements are met. It is unethical for local researchers to collect samples without ethical approval and to export them without relevant permits. On the other hand, receiving and using samples that do not have ethical approval and were not authorized for export is equally unethical.

5.3 Standard of care: during and post-study (if applicable)

Standard of care is not universal; hence if collaborative research involves different countries and the issue of standard of care of research participants is applicable, there should be agreement as to which standard of care would be used in the various countries. This issue should be covered in the protocol so that the relevant Ethics Review Committees consider it when they review the protocol. If applicable, the issue of standard of care post-study should be similarly dealt with upfront; it may be necessary to explore possibility of forming partnerships with other stakeholders such as ministries of health, non-governmental organizations and the private sector in order to address the issue of sustainability of post-study care of participants. It should be emphasized the issue of standard of care needs to be considered on a case by case basis taking into account various factors such as the nature of health condition under investigation, status of public health care system in the country where participants are to be recruited, sustainability of proposed standard of care and potential partnerships with other stakeholders.

5.4 Capacity building

One of the reasons for engaging in collaborative research is inadequacy or lack of appropriate expertise. It is therefore imperative that the issue of capacity building be addressed. Thus an assessment of capacity deficits at the levels of personnel and institutions should be done and a plan of capacity building activities should be included in the protocol and other relevant documents such as MOUs and contracts. It should be acknowledged that some needs such as infrastructural needs of institutions may be beyond the ability of researchers and their sponsors to fully address hence there may be need for partnerships with other relevant players.

The ultimate goal of capacity building should be to enhance the capability of local researchers and their institutions to conduct high-tech research without having to ship samples to laboratories in foreign countries. Collaborations could still continue, but with the collaborating institutions carrying out their part of the research at their local institutions. An efficient system of technology transfer could facilitate the global advancement of health research, which in turn could contribute towards the improvement of the health of mankind.

5.5 Sharing and ownership of samples: during and post-study

The issue of ownership of samples shared by researchers and their institutions in a collaborative research is critical and should be clarified before the samples are collected and pooled together. In some cases, archived samples are contributed towards the pool of samples for collaborative research. The archived samples may have been collected for routine diagnostic and/or therapeutic purposes and not for research purposes. If samples are to be shipped from one country to another, Material Transfer Agreements (MTAs) with appropriate conditions and specifications should be developed. It is the responsibility of the custodians of samples to ensure that MTAs that adequately address all pertinent issues are in place before the samples are released.

5.5.1 Some ethical issues

There are several ethical and practical issues that need to be addressed;

- Do the samples belong to the PI alone or to the PI and all the collaborating co-PIs?
- If some samples are going to be stored beyond the life span of the collaborative research project, who owns them post-study?
- What about the institutions where the researchers are based, do they have any legal claim over the samples collected by their employees?

- Whose responsibility is it to provide funds for continued storage of samples post-study?
- If archived samples are to be used, what were they originally collected for?
- If the archived samples were originally collected for research purposes, was consent given for them to be stored for future research?
- If so, was the consent given for a particular disease or any other disease?
- If the archived samples are owned by the institution where they are stored, will the institution surrender its ownership to another player involved in the collaborative research?
- If samples are to be shipped to another country and there are some 'leftovers', should they be destroyed in the foreign country or should they be shipped back to the country that donated them?
- Samples could be kept with personal identifiers, which mean that the donors of the samples can be identified. Personal identifiers include names, addresses, national identification numbers and telephone numbers. The risk of compromising privacy and confidentiality of sample donors is relatively high when personal identifiers are retained.
- Samples may be reversibly de-linked from the sample donors, but the de-linking code is kept so that it remains possible to trace the data to the individual donors. Reversibly de-linking samples helps to enhance protection of the privacy and confidentiality of sample donors while enabling possible future analyses that may require samples stored data to be linked to the individual sample donors. One practical challenge is the mechanisms of keeping the de-linking code and sustainability of such mechanisms especially when the particular research project that collected samples and generated the data is over.
- Samples may be irreversibly de-linked samples: the de-linking code is not kept but is destroyed.
- Samples may be anonymized in the sense that no personal identifiers were obtained in the first place.

5.6 Data sharing policy: during and post-study

Collaborating researchers should agree on the mechanisms of sharing data that is generated through the collaborative research. The data sharing policy should cover such issues as storage of the database, mechanisms of accessing the data during and/or post-study, protection of privacy

and confidentiality of sample donors and potential future use/analysis of the data. Mechanisms agreed upon may have budgetary implications which should be addressed upfront.

The nature of samples from which the data were obtained has a bearing on the data sharing mechanisms. As explained in section 5.5, the samples could be linked to sample donors, reversibly de-linked, irreversibly de-linked or anonymized. Thus data sharing policy should take into account agreements pertaining to the sharing and handling of samples from which the data were derived.

It should be noted that whereas most developed countries have legal frameworks and guidelines specifically meant to enhance protection of various types of data, the majority of developing countries do not have appropriate laws or guidelines in place. In the context of international collaborative research involving developed and developing countries, it is therefore critical that the issue of data sharing is dealt with upfront by all the stakeholders. It is also important for countries that still do not have appropriate regulatory frameworks to work towards the development of such frameworks in order to ensure adequate protection of data while promoting the much needed health research.

5.7 Intellectual property rights

Although currently there is debate on the potential impact of Intellectual Property Rights (IPR) and patents on the health status of developing countries, IPR and patents remain valid legal tools that are recognized globally. Most industrialized countries and pharmaceutical companies make use of IPR and patents to protect investments made in Research and Development (R&D). International collaborative research sometimes involves researchers from developed and developing countries, and in some cases pharmaceutical companies are part of the stakeholders.

It is therefore critical that researchers have a reasonable understanding of IPR and patents; as players in collaborative research the results of which could be commercializable researchers need to be aware of the fact that some inventions and scientific discoveries qualify to be intellectual property that could be protected by law through patents. Mere collection of samples or mere participation in a research project based on a protocol developed by someone else may not be patentable, even if the research project could lead to an invention or scientific discovery. As employers of researchers, institutions should have in place institutional IPR policies that should take into account the advent of international multi-centre collaborative research. It is always advisable to consult relevant experts for advice and guidance.

5.8 Information dissemination and authorship

Methods of disseminating information pertaining to collaborative research need to be spelt out, with roles of various players clearly stated. It is important to have a systematic and organized way of disseminating information, rather than a haphazard, free-for-all approach. Methods such as community engagement activities, pamphlets, web-sites, newsletters, print media, electronic media, seminars, workshops and publications in peer-reviewed journals could be used. Public engagement is important because it gives the researchers an opportunity to disseminate accurate information about their research.

5.8.1 Some ethical and practical issues

Conducting research without disseminating findings to the wider scientific community as well as to the participating communities is unethical. One method of disseminating information is through peer-reviewed publications. Since collaborative research may involve many researchers from different institutions and different countries, authorship of peer-reviewed publications could pose some ethical and practical challenges. Some of the issues are listed below;

- A few members of the collaborative research team could monopolize the publications and wrongfully leave out other deserving researchers from the authorship.
- The other side of the above challenge is 'ghost authorship', which means that names of people who do not deserve to be authors because they did not contribute anything to the manuscript are included. In some cases this is because for strategic and social desirability reasons, the PIs want to include certain 'influential' people. For instance, if the leading researchers are from the developed country they may want to include certain 'influential' or renowned people from the developing countries whereas if the leading researchers are from the developing countries they may want to include names of certain 'influential' people from the developed countries for various strategic reasons.
- Another case of social desirability is where a researcher participating in a collaborative research project may want to include the name of his/her boss or head of institution even if the boss or head of institution does not deserve to be an author.

6.0 CASE STUDY: DATA SHARING IN AN INTERNATIONAL COLLABORATIVE RESEARCH PROJECT

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International collaborative consortium

In order to collect adequate samples to achieve a significantly high statistical power in a population-based genomic epidemiological study, institutions in developed and developing countries formed a consortium in a 5 year project. A coordinating centre was established at an institution in one of the collaborating developed countries. Due to lack of adequately equipped laboratories in the developing countries, the local collaborating investigators in the developing countries collected samples and shipped them to the institutions in the developed countries where genotyping of the samples in high-tech laboratories could be performed. In order to enable genetic associations to be calculated, corresponding clinical data and sociodemographic data for the samples were also submitted to the coordinating centre of the consortium.

Data sharing policy of the consortium

The coordinating centre established a database for the genotypic data generated from the samples, as well as for the clinical and sociodemographic data submitted by the collaborating institutions. Each collaborating institution could access genotypic data for the samples it submitted, but not genotypic data for the pooled samples from the various collaborating institutions in the developing countries. Similarly, each institution could access its own clinical and sociodemographic data, but had no access to the pooled clinical and sociodemographic data. The coordinating centre had access to all the pooled data of the consortium.

Divergent schools of thought regarding the data sharing policy

At a meeting of the consortium collaborators, Professor Bomba Kabisa, one of the local collaborating co-principal investigators based in one developing country, indicated that she was not happy with the fact that local collaborating institutions did not have access to the pooled data in the database, during and after the consortial project. She felt that whereas the coordinating centre could continue using the pooled data long after the 5 year life span of the consortium, the individual collaborating institutions and their local collaborating investigators would not have access to the pooled data. She felt that from the point of view of her institution, such lack of access to the pooled data negated the whole purpose of forming a consortium in the first place.

Although a few investigators supported her view, the majority of the investigators from the developing countries were of the view that looking beyond the 5 year period of the consortium was unreasonable. They argued that it would be practically cumbersome to manage such continued access to the database by all collaborators after the expiry of the project. They felt that the local collaborating investigators from the developing countries should be content with such benefits as injection of research funds into institutions in the developing countries, post-graduate scholarships for students from the developing countries, possibilities of being co-authors of peer-reviewed publications and opportunity to be associated with an international research consortium.

Some questions to guide discussion

1. Which school of thought do you support, and why?
2. How would the data sharing policy that you support be implemented?
3. For the school of thought that you agree with, what ethical principles could help to support your position?
4. Who should be involved in the determination of an appropriate data sharing policy for such a consortium as the one in this case study?

7.0 REFERENCES

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