Research Ethics in Africa: A Resource for Research Ethics Committees

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Furthermore we want to acknowledge the administrative assistance of Bronwyn Coombs, who provided initial support, Alida Mombers for her organization skills during the workshop and Anita Fourie for her constant support.
Most maternal deaths (99%) occur in developing countries and 6.6 million children under five years of age died in 2012, mostly due to preventable diseases as they did not have adequate access to care.

Research is essential to address these common preventable diseases and provides evidence for cost-effective, affordable health care that is focused on the health problems of the particular region where it is being conducted. Unfortunately funding for research programmes is unaffordable for many African countries and historically Africa has had to rely on sponsors and researchers from high income countries to initiate and fund most of the health research that has been done over the last few decades.

It is critical that research participants with limited access to choice in health care options and from poor socio-economic backgrounds, are adequately respected and protected during the research process. For this reason this book will be a very useful resource for research ethics committees in Africa, who need to ensure that human participants are protected in health care research processes.

Furthermore, it is heartening that the book has been written by scholars from Africa, whose shared vision is the protection of human research participants in research. These authors have sought additional research ethics training to fulfil this duty. Their drive to do so comes from a personal commitment to the people of Africa. The book also aims to highlight research ethics issues from an African perspective accepting and acknowledging that many aspects and principles of research ethics are universal in scope.

I do hope that you, the reader, will share in the passion of these authors to ensure the protection of research participants in Africa.

Archbishop Desmond Tutu
November 2013
PART I

RESEARCH ETHICS
IN AFRICA
The aim of this book is to provide research ethics committee members with a resource that focuses on research ethics issues in Africa. The authors are currently active in various aspects of research ethics in Africa and the majority have been trained in the past by either the Fogarty International Center or Europe and Developing Countries Clinical Trial Partnership (EDCTP) sponsored bioethics training programmes.

In this book we use the term Research Ethics Committee abbreviated to REC. However, this term can be considered as identical in meaning and interchangeable with many similar terms such as Institutional Review Board (IRB), Ethics Review Board (ERB), Ethics Review Committee (ERC) and others. What all these terms are referring to is a formally constituted group of suitably qualified persons who have a mandated authority (institutional or national) to review (primarily from an ethics perspective) and approve research involving human participants.

We gladly acknowledge the assistance of EDCTP for funding this book, including funding for a workshop held in August 2011 where the contributors met to discuss the research ethics issues and challenges they face as researchers and REC members from countries throughout Africa. The issues discussed and debated at this forum have translated into the different chapters in this book. There are four sections. The first focuses on an overview and historical background of research ethics in Africa, including a chapter on the mapping of current RECs in Africa. The second section discusses functions of RECs and provides guidance for the process of ethics review, standard operating procedures and safety monitoring. The third section addresses specific topics, including informed consent, vulnerable populations, participant remuneration, and the handling of biological samples. The final section focuses on resources needed by ethics review committee members and includes review templates, as well as a chapter on training opportunities for members.

The foundational principles in this book are based on the three principles published in the Belmont Report, namely Beneficence, an obligation to do good and not to do harm, Justice in performing and distributing both the benefits and the burdens of research, and Respect for persons (autonomy) during the entire research process, from development to translation of results into action. (1) Respect for persons in research translates
into seeking the individual consent to participation and is based on the concept of independent or individualistic personhood. Informed consent therefore requires first-person consent, which is the universally acceptable standard. This may be problematic in societies with a communitarian view of personhood as is often the case in Africa. (2) This uniquely African perspective is discussed in some of the chapters in this book.

Many of the chapters also refer to the ‘Eight Benchmarks of Clinical Research’ first published by Emanuel et al. (2004) and now widely utilised within a research ethics context. The eight benchmarks will not be discussed in any detail in the introduction as they are woven into many of the chapters you will find in this book. Briefly they are: Community engagement, scientific validity, social value, fair selection of participants, independent ethics review, informed consent, risk benefit assessment and respect for persons. (3)

We hope that our colleagues in Africa will enjoy reading this book and that it will assist in the vital task of human research participant protection in Africa. Although it was written primarily for an African research context we think this book will also be of value to researchers and REC members in other developing world countries. The book will also benefit researchers, sponsors and REC members from countries that sponsor research conducted in Africa.

REFERENCES

INTRODUCTION

The past few decades have witnessed significant growth in health research in Africa, in response to the serious health challenges of the continent, of which developed countries funded a significant proportion. This increase in the volume of research in Africa has not necessarily been accompanied by improvements in health research oversight systems, including ethical review committees, leaving the continent vulnerable to potential exploitative research funded by resource-rich countries. (1) This has raised concerns that researchers from developed countries may conduct research in Africa that cannot easily be done in their own countries due to a robust research regulatory framework there, which is often not found in most African countries. (2)

The abuses of human research participants in the western world has played a significant role in shaping present-day research protection norms, standards and requirements. (3) The unethical experiments that were conducted by Nazi scientists during the Second World War led to the formulation of the Nuremberg Code of research ethics in 1946, which has, since then, influenced the international research ethics environment in several ways. The Nuremberg trials led to the inclusion of a statement on voluntary participation in research in the Human Rights Charter of 1948. (4, 5) The trials also led to the promulgation of the Declaration of Helsinki by the World Medical Assembly in 1964, as well as to the development of the International Ethics Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guidelines) of 1982. (6) The UN Human Rights Charter, the Declaration of Helsinki, and the CIOMS guidelines, due to their international scope, have all significantly influenced the African research ethics landscape. (7)

1 Gabriel Mwaluko passed away suddenly in November 2013. His contribution to this chapter and volume is acknowledged and greatly appreciated.
The history of colonialism, as well as the internationalisation of research over the past decades, have significantly influenced research ethics standards in African countries. Some African countries have either established, or have remodelled their research oversight systems and committees on the US institutional review boards system, or in accordance with the World Health Organisation (WHO) guidelines on the operations of research ethics committees (RECs). Some countries have established a human research oversight system in response to the demands of research sponsors, and as a way of ensuring the eligibility of their institutions to receive research funding from certain organisations. In other countries, changes have been introduced due to the insistence of regulatory agencies of international research partners in their home countries. (7)

HISTORICAL EXAMPLES OF HUMAN PARTICIPANT EXPLOITATION AND ABUSE

Africa has not been immune to human research abuses, with numerous reports having documented unethical experimentation and unethical clinical trials in Africa. For example, in Zimbabwe, during the early 1990s, Dr Richard Gladwell McGown, a British anaesthetist working in Zimbabwe, was charged with conducting dangerous human experiments. He was arrested on allegations of having carried out medical experiments on 500 patients, of whom the majority was black. Having been charged with murder, Dr McGown was found by the courts to have conducted interventional studies, using new drugs and anaesthetics, without the approval of the National Drugs Authority, and without the knowledge of his patients. Allegedly, up to six of the patients died as a result of the experiments. (8, 9) A Harare court found him guilty of professional negligence.

In Nigeria in 2001, 30 families sued the Pfizer pharmaceutical company over trials of trovafloxacin (Trovan), an antibiotic that was intended to treat meningitis. In 1996, Pfizer flew a team of doctors from the USA into Kano, Nigeria, to test Trovan, an experimental drug, against bacterial meningitis. The new drug was tested on nearly 200 children during a meningitis outbreak. The trial compared Trovan with the recommended drug Ceftriaxone. Unfortunately children in the control arm allegedly received Ceftriaxone at an inadequate dose. Eleven children died, while some survivors suffered permanent brain damage and paralysis. During investigations, it was found that the clinical trial had not not been approved by a local research ethics committee, and that the families concerned were not adequately informed that their children were research participants in a study employing the use of Trovan. (2, 10) The families sued Pfizer through the US courts, resulting in an out-of-court settlement, but with Pfizer having to pay substantial compensation to them.

Another example of research conducted without either research ethics approval or individual informed consent is the study, conducted by Dr Bezwoda, testing the efficacy of breast cancer chemotherapy in South African women. (11, 12)
The above-mentioned cases are, most likely, a small fraction of the number of research abuses that occur in Africa, as other cases might go unreported due to various reasons. Research in developing world countries such as Africa and India, may be deliberately conducted in these contexts due to the existence of weak regulatory systems and a relatively litigation-free environment, compared with countries like the USA. There is a tendency to under-report the side effects of test drugs. Volunteer participants are also happy in general to participate with what they regard as innovative medical breakthrough drugs. Some authors allege that pharmaceutical industries and research institutions conduct clinical trials in Africa with little or no consideration for ethics, or for the relevance of the drugs to the needs and pathology of the trial subjects involved. (13)

Besides the known cases of unethical research practice in Africa, the clinical trials that were conducted in Africa during the 1990s have led to some serious debates regarding comparative standards of research ethics in Africa and so-called first-world countries. Questions have been raised regarding access to treatment, standards of care, voluntariness of informed consent practices, control of tissue samples, cultural values, justice, and exploitation in general. (14, 15, 16) The majority of views expressed in said debates largely represent the opinions of scholars from the developed world, with little contribution being made from those in Africa. However, since the late 1990s, African bioethicists and philosophers have authored a significant number of publications on many issues relating to the ethical conduct of research. Critics have further observed that the informed consent process is often not optimal, and that therapeutic misconception plays a significant role in recruitment. (See Chapter 11 for additional discussion of this concept.) REC members who are not well versed in the principles of research ethics might be persuaded to approve ethically risky research, in order to ensure that their institutions receive a variety of benefits as a result of collaborating with international institutions or sponsors. (13, 14, 15)

The above-mentioned examples are but a few of the many that indicate that, without a robust research oversight system, researchers and research staff might disregard ethical principles, national laws and international guidelines, either inadvertently or deliberately.

The Development of Research Ethics Systems in Africa

Research oversight capacity is critical for the protection of human research participants, as well as to prevent exploitation of African populations, communities, institutions, and countries. RECs, which are one part of the research oversight system, have an obligation to safeguard the welfare of research participants. The first documented cases of ethical review in African health research were recorded in South Africa (SA). The University of the Witwatersrand established a health REC in 1966, and over the last three decades most
tertiary institutions in SA have established RECs. Currently, there are approximately 45 local RECs in SA, including two in private, non-academic institutions. (17)

In relation to RECs, several other African countries have followed suit, having established research oversight systems at varying levels. For example, the Medicines Control Council (MCC) of SA was established in 1965 on the prescripts of the Medicines and Related Substances Act, 1965 (Act no. 101 of 1965). (18) Both SA and Zimbabwe established MRCs, in 1969 and 1974 respectively, to regulate research by means of serving as a review body for health research. (19, 20) The National Institute for Medical Research (NIMR) in Tanzania was established by the Parliament Act No. 23 of 1979 as a parastatal body under the Ministry of Health to regulate and coordinate health research. (21) In Kenya, the Kenya Medical Research Institute (KEMRI) was established in 1979 through the Science and Technology (Amendment) Act of 1979, as the national body that is responsible for carrying out and for regulating health research undertaken in Kenya. (22) Some countries, like SA, now have legislation in place that provides for research oversight systems, including obligatory ethical review, as well as national guidelines. (17, 23, 24) The SA system is similar to the USA system with the SA Department of Health, the National Health Research Ethics Council (NHREC) and the Medicines Control Council (MCC), the equivalent of the USA’s Department for Health and Human Services (DHHS), Office for Human Research Protection (OHRP) and Federal Drug Agency (FDA). The mandate of the current NHREC is the oversight of all health research. Kenya also developed national guidelines in 2004 (National Council for Science and Technology Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya), followed in 2005 by the Ministry of Health Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines. (24, 25, 26) Of particular importance in Africa is vaccine research, especially in view of the HIV epidemic. Currently only SA’s Medicines Regulatory Authority (MRA) is capable of adequate provision of national oversight for vaccine research, while other national MRAs need to be strengthened or established. (27, 28)

Such oversight systems have evolved over the years in both scope and complexity, with some countries now having well-developed, decentralised ethical review systems, whereas others have centralised systems, in accordance with which all health research is approved by a single REC. Various ethics review models are utilised on the African continent, namely a local model, with either institutional or regional review; a centralised model, with ethics review and approval at national level; and a private model, in terms of which researchers can obtain ethical approval from a private (fee-for-service) REC. Although such models already exist in such countries as SA, Zambia, and Cameroon, they are not common in other African countries. (27, 29)

In November 1999, the African Malaria Vaccine Testing Network sponsored a seminar on health research ethics (HRE) in Africa at Arusha, Tanzania with the objectives of identifying the health research needs and priorities in sub-Saharan Africa, and to
study the mechanisms used for the ethics review and monitoring of research in the region. (30) Reports by country representatives revealed several problems with the review and monitoring of health research in the region, including the following:

- inadequately developed ethics review committees (erratic meetings, poor leadership, etc.);
- lack of resources (computers, office space, etc.);
- limited or outdated legislation;
- overworked, and/or untrained committee members;
- low awareness of ethics guidelines, and
- lack of training in bioethics and research ethics.

These problems are evidence of underdeveloped research oversight systems that are characterised by limited funding, insufficient training and inadequate standard operating procedures (SOPs). (28) A need, therefore, exists to address the challenges on an on-going basis if HRE review systems in Africa are to improve to the point where they can meet internationally acceptable standards and levels.

As a follow-up to the above-mentioned workshop, the African Malaria Network Trust (AMANET) in 2007, with the support of the Bill and Melinda Gates Foundation, conducted an extensive and comprehensive survey of 31 RECs in Africa to identify some institutional needs in HRE. The methodology of the survey included the use of self-administered questionnaires and face-to-face interviews. The results of the survey, with regard to the surveyed committees, showed: the majority (22 out of 31) were institutional; 10 out of 29 lacked guidelines; 8 out of 27 lacked SOPs; 7 out of 19 had never revised their SOPs; 10 out of 28 lacked training for members on joining; 15 out of 28 lacked continuing training of members; 10 out of 26 paid their members a sitting allowance; and 28 out of 28 lacked electronic data management and archiving systems.

From the survey, the resources that were available to RECs generally included office space, computers, office furniture, printers, internet access, email facilities, telephones, and filing cabinets. Electronic data management and archiving systems were not available to any of the RECs that responded to the survey. Among the constraints facing the surveyed RECs were insufficiency of resources to operate REC, inconsistent participation by members, lack of recognition of the role played by RECs, pressure from researchers and sponsors, insufficient expertise regarding ethical review, inadequate institutional support, and lack of complete independence. (22) Overall, the survey found variations in oversight levels in the various institutions and countries covered by the survey. After the survey, AMANET initiated a capacity-strengthening programme to address the gaps identified. The programme composed of capacity-strengthening sub-grants for RECs, HRE training workshops for REC members, advanced HRE training workshops for investigators, web-based HRE and web-based HRE discussion fora. (31)
Besides AMANET, various other organisations have been actively involved in building research ethics capacity in Africa. For example, the Fogarty International Center at the National Institutes of Health (NIH USA) initiated a programme to provide grants for research ethics capacity building. The grants programme was initiated following discussions at the first Global Forum on Bioethics, which was held in Bethesda, USA in 1999. During the Forum, it was noted that there were disparities in research oversight systems globally, and that the need existed to build capacity in research ethics and ethical review to ensure that all research participants were equally protected. To date, 12 programmes, recruiting scholars from African countries, have been funded (see chapter 22). Said programmes have contributed significantly to research ethics capacity building in Africa by training a total of more than 300 long-term trainees at various levels, including certificate, diploma, master’s and doctoral. The various training programmes have also been offering short-term training opportunities in the form of workshops.

The European and Developing Countries Clinical Trials Partnership (EDCTP) is also a major supporter of research ethics capacity building in Africa. EDCTP has, since 2005, funded several research ethics projects in Africa. EDCTP specifically provides grants for strengthening the cause of ethical review in Africa. The grants support research ethics training and the building of REC capacity. The Welcome Trust, a UK-based charity organisation, has also committed considerable funding to researching ethics research, as well as smaller amounts for training and workshops in developing countries, including those in Africa. There are various other capacity-building initiatives, including the Training and Resources in Research Ethics Evaluation (TRREE). TRREE is an online training resource that is aimed at limited resource settings. The Council on Health Research for Development (COHRED) in 2010 initiated the MARC project, which was aimed at mapping research ethics committees and drug regulatory bodies across Africa, providing a platform that could be used to enhance communication between the committees and the national MRAs (See chapter 3). The WHO has also put in place some programmes for strengthening the coordination of RECs in developing countries, including those on the African continent. (27)

At the highest level of political governance on the African continent, the African Union (AU) has signed the African Charter, as well as the Protocol to the African Charter on Human and People’s rights on the Rights of Women in Africa.3 The aforesaid important documents seek to prohibit all experimentation without the prior individual informed consent of all participants, as well as all due consideration of women’s rights, during

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2. A list of all research ethics capacity development EDCTP-funded programmes can be found at http://www.edctp.org/Project_Profiles.245.0.html?&no_cache=1 (Accessed 28/01/2012).

clinical trials. (32, 33) The linking of informed consent to human rights is evidence that accountability in medical experimentation in Africa is seen to be of paramount importance, and is certainly increasing. It remains to be seen how the various countries in Africa will convert the Charter into action. The AU, through the United Nations Economic Commission for Africa (UNECA) has also been working on an initiative that is aimed at promoting the strengthening of research coordination and oversight in Africa.

CONCLUSION

Events in other parts of the world have clearly played a significant role in directing the development of the research ethics environment in Africa. The majority of African countries have some kind of system in place for the ethical review of health research. In some countries, the systems are supported by legislation, whereas they are still informal in others. The cases of human research abuses in Africa discussed above are evidence of the need to strengthen research oversight protections in Africa still further, in order to ensure that vulnerable populations are protected. RECs are just one important component in the entire system of human research protections. Countries and institutions should put in place measures to ensure the protection of research participants. It is imperative that systems be enhanced across Africa, so that all African citizens are protected from research-related abuses. Doing so will also minimise the potential for researchers from developed nations to exploit research populations in Africa. The AU and WHO can play an important role in establishing and in enforcing standards that require adherence by all countries. Some African-specific issues require special focus. The following questions must be considered: Does research address community needs? Does research focus on national priorities? Is there a national research agenda? Are researched communities involved in identifying research problems, setting research priorities and developing research protocols? Do research findings make a difference to the targeted beneficiaries? Many such issues are discussed in some detail in the other chapters of this book.

REFERENCES

19. www.mrc.ac.za/about/mrcact.htm (Accessed 31/03/2014)
INTRODUCTION

Currently, health research initiatives worldwide are increasing in both scope and complexity, especially in developing countries. (1) The increase in the number of health research activities in African countries necessitates sound ethical review structures and functions in the form of research ethics committees (RECs). REC review of health research protocols is acknowledged as being the cornerstone of international guidelines regarding research involving human subjects. (2)

The MARC (Mapping African Research Ethics Review Capacity) Project, a three-year initiative funded by the European and Developing Countries Clinical Trials Partnership (EDCTP; www.edctp.org), aimed to develop an interactive, web-based resource map of Africa’s RECs, indicating REC capacity and capacity-building initiatives. A secondary objective of the MARC Project was to map medicines regulatory authorities (MRAs), and to facilitate better links between MRAs and RECs. MARC received supplementary funding from Pfizer (www.pfizer.com), and from the Fogarty International Center of the US NIH, through the South African Research Ethics Training Initiative (SARETI; www.sareti.ukzn.ac.za/Homepage.aspx).

The Council on Health Research for Development (COHRED) in Geneva, Switzerland (www.cohred.org), in collaboration with SARETI at the University of KwaZulu-Natal in South Africa, developed MARC. EDCTP supported MARC, since the key to developing medicines (including clinical trials), interventions and medical technologies in and for Africa is the effective and efficient ethics review of health research. As MARC is an interactive, web-based platform that uses COHRED’s Health Research Web (HRWeb) platform (www.healthresearchweb.org), all HRWeb facilities that are available to RECs
and MRAs in Africa will also be available to any REC globally, contributing to the effective ethics review of health research globally.

Several empirical studies have highlighted the need for ongoing research ethics capacity building on the continent. (3, 4, 5) Ethics review, and subsequent monitoring of health research, require adequate resources and expertise, being capacities that are limited in various ways in most African RECs. Many challenges facing RECs not only affect the competence of RECs in processing reviews and approvals, but they also significantly weaken their ability to provide quality health research oversight. (6) There is, thus, a need for tools to facilitate the administration of the committees and to enable them to streamline their protocol review procedures. In this regard, MARC Web (www.researchethicsweb.org) is an African-based resource that facilitates a systematic platform to assist in building up the standards and quality of RECs and ethics review in Africa, in addition to linking these RECs to global research ethics resources and exchanges.

Mapping of RECs in Africa

The three components of the MARC project are: 1. the online mapping of RECs; 2. the mapping of capacity-building efforts in research ethics in Africa; and 3. the mapping of Medicines Regulatory Authorities (MRA) in Africa.

The REC information mapped consists of: 1. basic contact information; 2. capacity information that provides detailed quantitative insight into the functions, capacity, resources and needs of the respective RECs; and 3. REC support documents. See Table 1 below for specific details.

Table 1: Format of REC information currently available on HRWeb8 (with permission from Ijsselmuiden et al)

<table>
<thead>
<tr>
<th>BASIC LEVEL INFORMATION</th>
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</thead>
<tbody>
<tr>
<td><strong>Institutional details</strong></td>
</tr>
<tr>
<td>Institution name</td>
</tr>
<tr>
<td>Type of REC</td>
</tr>
<tr>
<td>Personnel details</td>
</tr>
<tr>
<td>Chairperson name</td>
</tr>
<tr>
<td><strong>Contact details</strong></td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>Email</td>
</tr>
<tr>
<td>Telephone</td>
</tr>
<tr>
<td>Protocol procedures</td>
</tr>
<tr>
<td>Operational language</td>
</tr>
<tr>
<td>Preferred manner of receiving protocols</td>
</tr>
<tr>
<td>How often REC meets to review protocols</td>
</tr>
<tr>
<td>How long in advance protocols need to be submitted</td>
</tr>
<tr>
<td>Written documentation regarding submission &amp; review procedures</td>
</tr>
<tr>
<td>Member details</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number of qualified ethicists</td>
</tr>
<tr>
<td>Number of women</td>
</tr>
<tr>
<td>Age distribution</td>
</tr>
<tr>
<td>Individual member details:</td>
</tr>
<tr>
<td>Years on REC</td>
</tr>
<tr>
<td>Term of office</td>
</tr>
<tr>
<td>Term of office for members of REC</td>
</tr>
<tr>
<td>Whether term of office is renewable</td>
</tr>
<tr>
<td>Training requirements</td>
</tr>
<tr>
<td>Whether members require specific training in the ethical review of research</td>
</tr>
<tr>
<td>How many members have had formal training</td>
</tr>
<tr>
<td>Finances</td>
</tr>
<tr>
<td>Whether the REC has a dedicated budget</td>
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<tr>
<td>Whether members are remunerated for their work</td>
</tr>
<tr>
<td>Facilities</td>
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<tr>
<td>What facilities the REC has</td>
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<tr>
<td>Telephone</td>
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<tr>
<td>Administration</td>
</tr>
<tr>
<td>Position of administrator:</td>
</tr>
<tr>
<td>REC procedures</td>
</tr>
<tr>
<td>Whether the REC has written operating procedures</td>
</tr>
<tr>
<td>Whether the REC has written guidelines to assist researchers</td>
</tr>
</tbody>
</table>

To date, 170 African RECs have uploaded their details on MARC, with an additional 1 100 from other continents – see Table 2 below for details. More specific information on governance, policies, national research priorities, financing, partnership and other relevant documentation will be uploaded to the site once the basic details of all identifiable African RECs have been entered onto MARC. MARC simply provides increased exposure, a means of directing researchers and other interested parties to each REC’s own primary website, and which maintains an active website featuring such information. MARC also hosts a virtual website for RECs that lack their own website, which is a site where interested parties can find out more about the REC concerned. The MARC website is also a valuable tool for RECs to use for assessing and reviewing their achievements in terms of targets and progress within their own committees. Furthermore, sharing the SOPs and policies of various neighbouring RECs should foster harmonisation and communication between RECs, and encourage renewed dialogue and exchange on current issues to do with ethics review in Africa. The MARC website has numerous benefits for researchers, donors and RECs, and should come to grow and evolve in response to the needs of such groups.
The MARC website, supported by Health Research Web (HRWeb) (www.healthresearchweb.org), uses a wiki-type approach that allows interactive and self-updating networking and knowledge sharing in real time. Certain parts of the site can only be uploaded or changed by ‘owners’ of the information concerned, and is therefore labelled as ‘semi-wiki’. For example, RECs can upload their details regarding the frequency of review, which data, however, other users cannot change. Any disagreements with the information provided can be entered on the discussion pages to allow for it to have an impact over time.

African RECs

MARC, since its initiation, has used snowball methods for initial and ongoing contact with operating RECs in Africa. At the time of writing, one hundred and seventy (170) RECs had been identified as operating across Africa – with great variability in skills, membership, and levels of efficiency (www.researchethicsweb.org/). Table 2 below shows country-specific information in this regard.

Table 2: African RECs listed on MARC, by country (8) (with permission from Ijsselmuieden et al)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of RECs</th>
<th>Country</th>
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<tbody>
<tr>
<td></td>
<td>Level 1</td>
<td>Level 2</td>
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<tr>
<td>1 Algeria*</td>
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<td>2 Angola*</td>
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<td>3 Benin</td>
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<td>3</td>
<td>31</td>
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<tr>
<td>4 Botswana*</td>
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<tr>
<td>5 Burkina Faso*</td>
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<td>9 Central African Republic</td>
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<td>11 Comoros</td>
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<td>40</td>
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<td>13 Côte d’Ivoire</td>
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<td>19 Gabon*</td>
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<td>20 Gambia*</td>
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<tr>
<td>22 Guinea</td>
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The website uses a wiki-type approach that allows for interactive and self-updating networking and knowledge sharing in real time. Certain parts of the site are only updatable by the 'owners' of the information concerned, hence it is labeled as 'semi-wiki'. For instance, RECs can upload details about the frequency of review, which data cannot be changed by other users. Any disagreements with the provided information can be entered on the discussion pages to have an impact over time.

**African RECs**

MARC, since its inception, has utilized snowball methods for initial and ongoing contact with operating RECs in Africa. At the time of writing, 170 RECs had been identified across the continent, each with varying skills, membership, and levels of efficiency. Table 2 outlines country-specific information in this regard.

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MARC Web is an open access platform on which all can see what is happening in the research ethics landscape, and then work with that knowledge in real time. As the platform is open, it can be used by any other REC, country or region outside Africa as well. Based on the latter, Latin America is mapping its own RECs on HRWeb, with over 1 100 RECs having been logged to date of writing.

An important outcome of the MARC Project was the realisation that the administration of research ethics committees is a neglected component of review efficiency and quality, which are as important as ethics training for REC members. Armed with such insight, COHRED arranged the first African Administrators of Research Ethics Committees (AAREC) meeting in Botswana in September 2011, at which the need for a REC Management Information System was confirmed. A full report of the progress that has, so far, been made in this direction is accessible at www.healthresearchweb.org/files/AARECFinalReport.pdf.

COHRED’s HRWeb and MARC teams subsequently used the same engine of the MARC Web and Health research web to design an information management system (IMS) for RECs that manages and streamlines review procedures, proposal submission pathways and operational processes, which they named the Research for Health and Innovation Organiser (RHinnO). The primary objective of RHinnO Ethics is to provide RECs with a low-cost, secure, fully cloud-based solution, which is low bandwidth compatible, for managing and tracking the throughput of research ethics applications throughout the entire life cycle of the research project. RHinnO Ethics also provides quick, reliable ‘real-time’ data, tables and graphs that can be used to monitor, to evaluate and to communicate (www.rhinno.net). Future users of RHInnO Ethics will automatically receive updates, links, and information on courses and on international ethics guideline reviews on their home screens.

Another key goal of MARC is to facilitate communication and networking between RECs, especially for purposes of capacity building. A supplementary grant that was made to MARC through SARETI at UKZN from the Fogarty International Center of the US National Institutes of Health (NIH) enabled the establishment of a ‘professional social network/discussion’ function on the MARC website (for which one name is ‘EthiCALL’), which is intended to facilitate better communication between RECs and MRAs across Africa. Given its advanced functionalities, it will capacitate the less
capacitated RECs, which will allow RECs to review multi-centre trials jointly under closed forums. The EthiCALL is likely to be used by anyone who is interested in professional communication between RECs.

The specific anticipated benefits of the above are:

- To enable graduates and students from several major research ethics training programmes (e.g. SARETI, IRENSA, ARESA, WAB) in Africa to connect and interact on topical issues in research ethics.
- To promote connection and interaction between trainees and staff from RECs/IRBs in their home countries, and encourage the formation of local activity groups to find solutions to difficult and diverse research ethics questions through blogs, questions, answer lists and online discussion forums.
- To provide ‘closed’/‘private’ forums that enable RECs to undertake joint review of multicentre trials. This special feature contributes to the empowerment of less capacitated RECs. It provides accelerated access to REC members, to ethics trainees and to other resource persons who are active in the field of research ethics and drug regulation.
- To provide, through low bandwidth internet access, access to the international expertise of research ethics experts in Africa and globally. REC chairs are no longer limited to the resource constraints of their own institution, and, depending on the prevailing local rules and policies, they have the ability to invite international experts to become online members of, or advisors to, their REC.

The success of this initiative will add a new dimension to African research ethics training and capacity-building initiatives. It might expand to create a virtual network of trained individuals, forming a pan-African research ethics discussion platform (with relevant information being accessible on the MARC website: www.researchethicsweb.org). MARC activities can also be followed on the Twitter social networking service at @MARC_Project.

As an index of its impact and future potential, the MARC/HRWeb initiative was positively noted and acknowledged in the landmark December 2011 report of the US Presidential Commission for the Study of Bioethics Issues, entitled MORAL SCIENCE – Protecting Participants in Human Subjects Research. The report, which was commissioned by US President Obama at the end of 2010, was released in December 2011. (7) A further MARC publication appeared recently in Developing World Bioethics. (8)

Mapping Medicines Regulatory Authorities

MARC’s secondary objective, which is to map MRAs in Africa, has been supported by an unconditional award from Pfizer. The mapping of MRAs provides a single portal for access to, and the identification of, MRAs, and improves visibility, transparency, ethical responsibility, and public trust. The mapping of MRAs can also contribute to their harmonisation in Africa, and it can help to accelerate the competent ethics review
of clinical trials, thereby increasing the efficiency of the research review systems in Africa. Hopefully, this work will supplement the work of UNAIDS’ AVAREF project. Progress thus far includes the mapping of contacts and basic procedural information from 26 African countries. (See * in Table 2.) MARC reduced its efforts to map Medicine Regulatory Authorities (MRAs) after NEPAD (New Partnership for Africa’s Development) started a new effort to harmonize MRAs in Africa.

CONCLUSION

The outlined achievements indicate MARC’s current and potential utility globally, suggesting that MARC is on its way to becoming the preferred international portal for locating and evaluating the RECs of developing countries. MARC will enable Africa, and others, to develop and sustain integrated and accountable research ethics review systems that will serve the aim of increasing both relevant and ethics research for promoting the health of Africa. MARC is a valuable tool for researchers, governments, research sponsors, and other stakeholders. Funding permitting, MARC is planning an extension to MARC II, with expanded objectives being set to improve the resources for relevant, ethical health research in Africa and the developing world. Collaborations and synergies with any other initiative aiming at the same goal are welcomed.

REFERENCES

PART II

THE RESEARCH ETHICS COMMITTEE


INTRODUCTION

The REC meeting is the core function of the REC. An REC should preferably meet regularly for face-to-face discussions, as the art of protocol review, from both a scientific and an ethical perspective, is essentially a learned process that is facilitated by debate and the discussion of research protocols at REC meetings. Relatively new members have the opportunity to learn by contributing to such discussions. Decisions made should thus be as a result of collective deliberation, rather than a matter of individual opinion. RECs that operate primarily via email curtail opportunities both for collective decision-making and for the on-going research ethics learning process that can be so rewarding for all REC members. The guidelines provided below are presented in point form to assist RECs in developing their own Standard Operating Procedure (SOP), as required and are based on the SOP of the Kenyan Medical Research Institute (KEMRI) REC (1):

- RECs should hold a series of scheduled meetings during each calendar year for the purpose of ethical review.
- The meeting schedule should be established in advance and sent to REC members at the beginning of each calendar year.
- The REC chairperson can convene special ad hoc meetings to provide expedited review of research proposals or applications, to address concerns regarding the rights and welfare of study participants, and to review unanticipated problems or issues of non-compliance.
- The REC members should be given final notification of the meeting, the agenda and the REC meeting in good time.
The minutes of each meeting should be recorded and confirmed at the next convened REC meeting.

The REC chairperson or REC secretary may invite a Principal Investigator (PI) to an REC meeting to present their proposal, elaborate on specific issues, or to offer clarifications.

The REC chairperson or REC secretary may also invite independent consultants to a meeting, or request them to provide written comments upon the review of an application that is subject to prescribed confidentiality agreements.

All core REC members must be present at each meeting, or must have provided their evaluation comments prior to the scheduled REC meeting.

No REC meeting should be held or should proceed without a quorum.

If a quorum is lost during a meeting, the REC should neither vote on, nor make a decision regarding a research proposal or application until the quorum is restored. If a quorum cannot be re-established, the meeting should end and be rescheduled.

An REC member should attend at least half of the scheduled meetings held in each calendar year. Failure to attend the required minimum may lead to the termination of the appointment of said member to the committee.

APPLICATION REQUIREMENTS

1. All applications for ethical review must be submitted before the prescribed deadline and all relevant documents must be submitted.
2. Only complete applications should be considered for inclusion on the REC meeting’s agenda.
3. The PI should submit an application for the ethical review of a research study.
4. Only one application for ethical review should be made for any research study.
5. All complete applications should be reviewed within a prescribed period.

PREPARATION OF THE AGENDA

1. The REC administrator/secretariat prepares the agenda for each scheduled meeting.
2. All complete applications that are received by the closing date should be assigned to the agenda, for consideration at the next scheduled REC meeting.
3. The REC administrator/secretariat designates reviewers for each application under REC consideration. Generally two reviewers are allocated to each project, one primary and one secondary. The primary reviewer takes the responsibility for presenting the project at the REC meeting and in some cases also takes the responsibility for reviewing the response from the applicant to the comments made by the REC. Obviously this arrangement is flexible and depends on the standard operating procedure of individual RECs. Both the primary and secondary reviewers must have neither a vested interest in the study, nor a conflicting interest.
4. The REC administrator should complete and close the agenda well before the REC meeting date.
ORDER OF THE MEETING

Although the following is a recommended order of agenda items, each REC can adapt the proposal to meet their own individual requirements:

1. Attendance/apologies
2. Declaration of conflict(s) of interest
3. Confirmation of minutes of the previous meeting
4. Matters arising from the previous minutes
5. Review of new proposals or applications
6. Review of amended protocols
7. Review of study status (progress) reports
8. Review of final study reports
9. Review of safety reports
10. Protocol deviation/violation notifications
11. Expedited review reports
12. Any other business
13. Date of the next REC meeting.

DECISION-MAKING

1. Following the deliberations on a given research proposal or application, the REC can make one of the following decisions at the meeting:
   a) It can approve the application.
   b) It can grant ethical approval, subject to specified conditions being met.
   c) It can defer making a decision on the research proposal or application until the reasons for the deferment have been addressed.
   d) It can defer making a decision until expert advice or opinion has been sought and received.
   e) It can request a resubmission of the research proposal or application, if substantive revisions are required.
   f) It can refuse to recommend ethical clearance, citing specific reasons that should be clearly communicated to the PI.
   g) It can appoint an ad hoc subcommittee to undertake further review of a particularly problematic submission. This subcommittee can be mandated to conclude the matter and communicate the final decision and findings to the PI or can report back to the full committee, the latter usually being preferable
2. The REC should reach a decision on the ethical suitability and feasibility of a given research proposal or application by consensus, or by vote.
3. Where unanimous decisions cannot be reached, the REC may request the provision of further information or the clarification of any issue(s) by the PI or applicant, or invite the PI/applicant to attend the next convened REC meeting.
4. REC members should also vote upon the recommendations made by the primary reviewers, according to the criteria for approval, whenever a consensus cannot be reached.
5. The REC may delegate to the REC Chairperson (or Secretary) the authority to approve research proposals or applications administratively, between meetings, if stipulated conditions have been met.

**COMMUNICATING A DECISION**

1. The REC secretary should inform the applicant, in writing, of the outcome of ethical review, as soon as possible. Two to five working days is a reasonable time period in which to do so, as any longer than one week should be avoided, where possible.
2. The communication must clearly explain the reasons for the determination, and outline the additional information or changes that are required.
3. The REC should encourage open communication with the investigators to resolve outstanding requests for information, or any required modification and clarification of ethical issues that are raised regarding a particular proposal or application.

**RECORD KEEPING**

1. All documentation and communication of the REC must be accurately dated, and filed in such a way as to allow for ease of access to documents in the future.
2. All documents received by the REC should be retained for a specified period following the completion of a study.
3. The following documents should be kept:
   - The agenda of the REC meetings;
   - The minutes of the REC meetings;
   - Copies of all proposed and approved research protocols, scientific evaluations (if any), approved consent documents, annual and status reports, and incident reports;
   - Copies of all correspondences between the investigators and the REC;
   - The records of continuing review activities;
   - The final report of the study;
   - The record of all site and/or audit visits;
   - All REC reports.

**CHALLENGES FACED BY AN AFRICAN REC**

Many RECs are challenged by a lack of resources, as well as by a lack of institutional capacity and, often, institutional goodwill. REC secretariats tend to be understaffed, with the result that administrative matters such as version control and non-technical requirements, like contact addresses, budget discrepancies, translations and time frames, are addressed in meetings - taking up valuable discussion time. Very little time is, therefore, left for the all-important activity of ethical review. In addition, many RECs lack sufficient reviewers to evaluate the numerous proposals that tend to be assigned
to them under very tight deadlines. Furthermore, review work is often perceived to be less taxing than the writing of protocols, and, in addition, the former is often not acknowledged in performance appraisals. The above-mentioned situation leads to a lack of motivation to review protocols exhaustively, and reduces the quality of the reviews produced. Allowing reviewers to send in their review reports, rather than having them attend meetings, compounds the quality issue by limiting the amount of constructive debate that is conducted on ethical issues.

**RESPONSIBILITIES OF AN REC MEMBER**

After determining the scientific importance of any given study, each REC member is responsible for doing the following:

- Review research proposals to determine the safety and well-being of human participants before each meeting, and making recommendations to ensure that the four principles of ethical review have been incorporated - ensuring that adequate time for review is allowed prior to the REC meeting;
- Attend meetings to debate issues and participate in the decision-making required to ensure the protection of human participants meaningfully;
- Declare any conflict of interest, and
- Keep abreast of international developments in relation to health and ethics issues.

Attending REC meetings is a key responsibility of members. Each member is carefully selected to ensure that a diversity of perspectives is represented when making ethical determinations. Consequently, discussion and debate at REC meetings is essential to ensure that research participants are adequately protected. In addition, in Africa decisions are usually arrived at by means of consensus, and not often by voting, although this is changing particularly as certain funders require that a vote be recorded for each project approved. This means that every perspective is of critical importance to the final determinations.

Important duties of RECs include the following:

- Routinely educating and training REC committee members to ensure the quality and consistency of review;
- Developing standard operating procedures for ethics review;
- Conducting and promoting education and training in research ethics for professionals;
- Liaising with other RECs in matters of common interest, and also supporting and facilitating the work of other committees on ethics issues;
- Informing relevant government agencies on matters that might have policy implications;
- Promoting community awareness, and
- Consulting with individuals, communities and the government on issues of ethics relating to research on human participants.
The REC also has responsibilities that can only be fulfilled with the support of their parent institution. If such support is available, an REC should participate in the ongoing monitoring of the conduct of research projects that have been approved to ensure that provisions in approved protocols are not varied to the disadvantage of human participants, once the project is under way.

In order to fulfil its role and responsibilities, the REC has the authority to:
- Demand modifications to the research protocol;
- Enforce and monitor all informed consent or patients’ rights issues, and
- Suspend or stop any research that is non-compliant.

The REC is the protector of human participants in research, and should ensure that the dignity, rights, safety and well-being of human participants are protected. At the macro level, it must ensure that scientific research based on experimentation on human participants also has social value and is in the national interest. It is, therefore, important for the individual REC member to realise that his or her role is very important, and should, consequently, be undertaken with due diligence and commitment.

RECOMMENDATIONS AND CONCLUSION

The REC is the conscience of the scientific research community, and the protector of human research participants. Its primary role is to safeguard the dignity, rights, safety and wellbeing of all actual and potential human subjects within the research enterprise. In this regard, it is of paramount importance for the REC to be correctly constituted and have all the resources that it requires to execute such an important duty. The following are all important actions that must be taken to ensure that the very best outcomes are obtained for human participants in particular, as well as for the research enterprise in general. The REC and its members, and the institution have an overall collective responsibility to:
- Build the administrative capacity of REC secretariats to enable them to process protocols for administrative issues, before they are reviewed by RECs;
- Provide recognition and support to REC members, in order to motivate them to review protocols thoroughly;
- Increase the number of committee members to reduce the workload of individual members;
- Classify protocols according to risk and accommodate or provide appropriate review accordingly.
REFERENCE


Additional Useful Resources for RECs

The REC Standard Operating Procedures in Africa

Joyce Ikingura, Caroline Kithinji

Key Message: Standard operating procedures (SOPs) are fundamental to the establishment and operation of the Research Ethics Committee (REC). After establishing an REC, comprehensive SOPs are essential to ensure the REC operates consistently and effectively and hence helps to promote the protection of human research participants in Africa.

Introduction

For Research Ethics Committees (RECs) to function adequately, they should have Standard Operating Procedures (SOPs), since these documents describe in a systematic manner the steps that constitute the ethical review process. SOPs should be clearly formulated in a logical manner and regular revision is necessary in order to address the emergence of new ethical issues. Each REC should develop their own REC-specific SOPs.

Background

Most African countries have established RECs according to the MARC project, although there are few empirical studies regarding African RECs (see chapter 4). (1, 2) Nyika reported in 2009 that 9 of 31 African RECs operated without SOPs. (3) The African Malaria Network Trust (AMANET) subsequently held a series of workshops for training REC members and assisted in developing SOPs for African RECs. (4)

Why We Need SOPs

The establishment of any REC should go hand in hand with the development of SOPs to guide its operations and to ensure protection of research participants. The value of SOPs is that these documents provide a transparent document that can serve to guide or instruct REC members and researchers alike. (4) In the global era of research, with multicentre collaborative health research being conducted in Africa, there is a need to
harmonise ethical review to promote consistency and ensure compliance with applicable ethical guidelines and regulations. Harmonised SOPs will assist with greater uniformity in ethics review, which is very necessary due to the diversity of RECs in Africa, and may also improve public trust in the process. The SOPs will lead to consistency in the handling of different situations and result in a reduction of errors. (4) It also provides clarity regarding the different responsibilities of the chair, the administrator and the other REC members. New REC members will be educated by using the SOPs as a reference document for the procedural framework of ethical review. The existence of and adherence to detailed SOPs also provides partial defence against lawsuits and a basis for addressing complaints.

**SOP FORMAT**

The template for SOPs in the WHO guidelines can be adopted as a standard, and countries may add specific country requirements. (5) The WHO template SOP has 10 sections. In an effort to develop a common format, AMANET in July 2010, conducted a SOPs harmonisation workshop, with the objective of involving African REC stakeholders in developing a comprehensive SOP format that addresses common issues. (4)

**UPDATING SOPS**

There is an increasing trend for collaborative research in Africa which is associated with an increase in the complexity of research studies. This complexity is due to the emergence of new diseases and technological developments. These new developments raise ethical issues that need to be examined closely. SOPs should therefore be updated regularly to address these issues and to comply with both national regulatory frameworks as well as international requirements, a finding confirmed by Nyika et al. (6) All RECs reviewing research funded by the US federal government, e.g. the National Institutes of Health (NIH) must ensure that their SOPs comply with the procedural requirements of the US Office for Human Research Protections (OHRP). (7)

**CATEGORIES OF STANDARD OPERATING PROCEDURES**

The SOPs should cover the following categories:

**Category A: Ethics Review Committee Membership**

The specific requirements for RECs may vary across institutions. Factors to take into consideration are representation from different groups, educational requirements, age, gender, training, and certification. For example in Tanzania, the NIMR Act No. 23 of 1979 specifies the requirements. (8) The WHO 2000 guidelines probably provide good
guidance for African countries. (4) The SOPs should discuss the roles and mandates, as well as the structure and responsibilities of REC members. Dissolution of the REC is also an essential component.

**Category B: Administration**

The SOPs in this category relate to the day-to-day functioning of the REC including application requirements and procedures, frequency of meetings and deadlines, format of meetings, agenda and minutes, communication and record keeping.

**Category C: Review Procedures**

The different types of review procedures must be clearly explained. These include procedures for full committee review, expedited review, continued review and protocol amendments. Decision-making procedures and co-opting of ad-hoc expert reviewers must also be included.

**Category D: Oversight**

SOPs are required for passive monitoring such as requirements for annual progress reports; active monitoring whereby the REC members physically visit the research projects in the field to assess if the projects are being conducted according to approved protocols, and report adverse events and any unexpected problems that occur during the course of the study.

The need to provide insurance for clinical trial participants also needs to be clearly stipulated in the SOPs so that ethical review for all clinical trials will include reviewing arrangements for clinical trial insurance of the participants.

Another aspect of research that also requires the REC to have clear SOPs is the frequent request to transfer both samples and data from African countries to other collaborating institutions abroad. The REC needs to have SOPs to guide the transfer and exchange of the materials and data. These are often contentious matters that need to be dealt with diligently.

**ACCREDITING ETHICS REVIEW COMMITTEES**

In each country’s ethical review system, there should be system whereby REC operations are systematically evaluated according to established criteria. The national institution that has a mandate to oversee all matters related to health research coordination could ideally take up this function. This central body would thus be required to set standards for establishing RECs and for the criteria that will be used to decide that a REC has the capacity to conduct ethical reviews and grant ethical clearance. The system can also use self-evaluations whereby RECs informally evaluate themselves. (See Chapter
The very activity of evaluation may be a valuable educational experience as members learn more about themselves, their colleagues, the REC’s purposes, functions, procedures and operations.

CONCLUSION

The Standard Operating Procedures are an essential component of the establishment and operations of a research ethics committee. The SOPs increase the credibility of the REC both from the perspective of the researcher community that makes use of the REC and from the perspective of the ‘public’ who ultimately constitute the population of research participants. The importance of good SOPs is now acknowledged by RECs in Africa. SOPs are a fundamental part of the ethical review system of proposed health research and are recommended by the WHO. The REC that has developed its own SOPs and is using them consistently should demonstrate increasing objectivity and impartialness in its work. By developing their own SOPs to suit their specific unique requirements RECs can ensure optimal functioning.

REFERENCES

1. COHRED MARC Project Newsletter, Issue 2, January 2011.
5. WHO Operational Guidelines for Ethics Committees that review biomedical research. 2000.
A Stepwise Approach to Protocol Review

Christine Wasunna, Elizabeth Anne Bukusi

Key Message: This chapter provides research ethics committee (REC) members with a step-by-step guide for conducting an ethical review of a health research proposal or protocol.

INTRODUCTION

The ethics review of a research protocol, involving human subjects, is a process that starts with the submission of an application to the research ethics committee (REC). After protocol submission the process of ethical review should follow according to the category of review required. The review categories are:

1. Initial review - review of a protocol before the research is initiated.
2. Continuing review - periodic review of a protocol after initial approval.
4. Exempt certification - some activities that meet a prescribed criteria may be exempted from continuing review after the initial review has occurred (this category may not be applicable to certain countries).

COMPONENTS OF A RESEARCH PROTOCOL

A research protocol is a document that provides detailed information on how a study will be conducted. Some prefer to call it the recipe of the study. The following list provides important elements of a research protocol (1):

- a background analysis, scientific question(s) and/or an hypothesis, with determination of the potential knowledge to be obtained;
- a description of the innovative nature of the proposed research study;
- a comprehensive literature review in support of the proposed study, including an assessment of previous studies;
- a statement of the specific objectives of the study in line with the FINER (Feasible, Interesting, Novel, Ethical, Relevant) criteria;
- a description of the research design and methodology (inclusion and exclusion criteria, study procedures, statistical validation of the sample size, study population, and analytical plan for assessing results);
- a description of the plans for capacity building and/or technology transfer in the course of the research;
- a description of agreements on intellectual property issues, prior to the commencement of the study;
- a determination of the duration of the proposed research study;
- a description of the location(s) where research will be conducted, as well as a justification for the site selection;
  - a description of research objectives as distinct elements of the research proposal.
- a description of the type and number of research participants, including a strategy for the recruitment and selection of research participants, with sampling strategy as applicable;
- a description of the statistical analysis plan supporting the production of statistically valid conclusions that justifies the research involving human participants;
- a description of the ethical considerations, including the procedures that will be used to protect participants from possible harm or minimise the identified risk of harm;
- a description of the work plan for the proposed research;
- a description of the limitations or pitfalls in conducting the proposed research and how they will be addressed or managed;
- a description of the resources, such as the funds, equipment and facilities, that are required for the research;
- a description of the data analysis plan clearly indicating how each of research objectives will be analysed;
- a description of the dissemination plan in terms of the participants and/or the participating community, as well as in terms of formal publication, and
- a description of the qualifications, role and responsibilities of each investigator in the research study and their suitability for the assigned task(s).

Other Relevant Materials

The following should be included in the complete research protocol package depending on the type of research:
- Copies of details of the new drug or device under investigation;
- The investigator’s brochure or other materials supplied by any pharmaceutical company or other sponsor;
- Details of the recruitment strategies. This includes copies of all the potential advertisements to be used (print, internet, radio, TV, or other means);
- Informed consent documents, including the versions translated into the local languages, the back-translation versions, and the appropriate certificates of translation;
- The assent form for minors and the corresponding parental/guardian permission form, including versions translated into the local languages, back-translation versions, and the corresponding certificates of translation;
- Letters of support, signed by an authorised individual from each of the collaborating sites;
- Copies of all questionnaire(s), interview(s), survey(s), and/or any standard tests to be used in the research process, and
An organogram of the Data Safety and Monitoring Board/Data Monitoring Committee structure.

REVIEW OF A NEW RESEARCH PROPOSAL BY THE FULL REC

The following issues should be considered when undertaking the initial review of proposed research. (4, 5) One or two REC members are usually tasked with conducting the initial review, producing a written report and providing feedback to the committee as the lead discussants. Emanuel et al. described eight benchmarks of ethical research, which provides a useful framework for ethics review. (6)

1. Study design

The REC should evaluate the study design with regards to both scientific validity and ethical considerations, which may affect the rights and welfare of participants. The REC may request an expert consultant to review the research protocol to ensure that no unnecessary risks are involved and that the project is scientifically and statistically sound and have the potential to produce valid results.

2. Risks and benefits (10)

The assessment of risk and benefit in research is discussed in detail in chapter 10. This aspect of the REC review is undoubtedly one of the most critical aspects. The REC must decide whether the risks posed by the research are acceptable in relation to the potential benefits both for the individual research participants and for the common good, i.e. those individuals or future patients who will benefit from the new knowledge gained.

3. Equitable selection of research participants

When determining if the selection of research participants is justified and equitable, the REC should consider the rationale for the study, the circumstances and location in which the study will be conducted and the possible layers of vulnerability the participants may be exposed to. In addition, the REC must assess if the benefits and burdens imposed on the study participants is unbiased. For research involving vulnerable groups, the reviewer should take into account the justification provided by the investigators for the involvement of the vulnerable populations and the special safeguards that have been

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1. Sections 3-7 are adapted in part from Brown University Policies and Procedures for the Protection of Human Participants in Research. www.brown.edu/research/brown-university-policies-and-procedures-protection-human-participants-research (Accessed 06/11/2013). Although Brown University is an American institution and not an African one, the process of research proposal review does benefit from a fairly standardised approach that is based on internationally accepted bench marks and principles.
proposed to ensure that the possibility of risk of harm is minimised and the potential for undue influence or coercion is eliminated.

4. Identification of research participants and ensuring confidentiality

In evaluating the strategy for recruitment of prospective research participants, the REC should examine the method that will be used for the identification, screening and enrolment of the research participants, the study’s eligibility criteria, whether or not payments will be made for participation in the study and the provisions for protecting the privacy of the participants and confidentiality of their data.

5. The informed consent process

The REC should carefully assess the scope of consent and the cultural considerations and in particular the following components of the informed consent process: when, where, and how consent is obtained, and any provisions for the on-going consent of research participants, for example, in mental health situations.

6. Qualifications

The REC should carefully examine the qualifications of the lead investigator, sub-investigators and key personnel involved in protocol development and/or in conducting the study to ensure that they are qualified to fulfil their different roles in the research process. Such an examination should include reviewing the procedures requiring specialised skills, licensure, accreditation, and/or experience of an investigator to perform the proposed procedures. In addition, the REC should consider the adequacy of the research sites to make sure that they ensure the safety of the research participants or request for the information from the lead investigator on the description of the facility in which the research will be conducted.

7. Additional review

The REC should determine, depending on the potential risks involved in the study, whether a research study requires additional review and monitoring procedures. This is discussed in detail in chapter eight.

EXPEDITED REVIEW OR RESEARCH PROJECTS

Some research projects may qualify for an expedited review process. This means that the project is considered to be of relatively low risk and can thus be reviewed and approved outside of the full REC meeting. The following kinds of research studies may be suitable for expedited review: (2)

- no use of deception;
- not a clinical drug trial;
• not a study involving minor children, prisoners, pregnant women, homeless people or impaired adults;
• not a study of illegal activities, and
• generally not a study that would be construed as sensitive, for example a study examining personal sexual behaviour.

If the research qualifies for expedited review, the REC chairperson will nominate REC members to undertake the review. Expedited reviews may be conducted on a ‘rolling’ basis, at the discretion of the REC chairperson and secretariat, on the submission of applications. Once all required documents have been received, the REC member conducting the review will, after considering the merits of the study, decide whether or not to approve the research and convey this decision to the chairperson. Changes and clarifications can be requested from the researcher prior to final approval of the project. The REC chairperson may evaluate each application for its eligibility for expedited review upon request by the lead investigator or his/her representative.

CONTINUING REVIEW

After the initial approval of the research by the REC, the progress of the project should be reviewed by the REC at least annually, but the REC can decide that more frequent review is required, based on the degree of risk associated with the research study. Continuing review or on-going monitoring of research is discussed in detail in Chapter 8.

REVIEW OF A PROTOCOL MODIFICATION OR AMENDMENT

Often, during the course of a research project researchers discover that they need or want to make minor or significant changes or additions to the approved research projects. Any such changes must be approved by the REC prior to implementation. The REC member conducting this review should: (7, 8, 9)
• identify what modification is sought, and the justification or rationale for the suggested amendment;
• determine whether the amendment warrants revision to the current approved protocol, in which case the revised version should be reviewed;
• determine whether the amendment involves revisions to the consent/assent documents, and whether the changes are reflected in the updated consent/assent documents that are provided for review;
• determine whether the enrolled study participants will be informed of the change(s) and how this will be done;
• determine whether the amendment involves changes to questionnaires and/or survey forms, interview questions, and recruitment materials, and confirm that the proposed changes are reflected in the updated documents;
determine whether the suggested modification alters the eligibility criteria for the study, and, if so, whether provision is made for obtaining the consent of the enrolled study participants once again;

- determine, where an investigational article is involved, whether the proposed change(s) will affect the drug preparation or administration, or the treatment plans (if applicable, determine in what way);

- determine whether the proposed change involves the removal or addition of an investigator from the research study, and whether the affected investigator(s) who has relinquished his/her position and responsibilities has provided written communication to that effect, whether the CV of the new investigator has been provided, and whether his/her role in the study has been defined;

- determine whether the amendment being submitted is as a result of a safety-related event, and, if so, whether the safety report has been filed;

- determine whether the proposed change is as a result of Data Safety Monitoring Board (DSMB) advice, and, if so, whether such a report or recommendation has been included in the application under review, and

- assess the risk/benefit status of the study, in view of the proposed amendments.

Changes to approved protocols can only be initiated after written REC approval has been obtained, except in cases where the modifications are necessary to eliminate apparent immediate danger to the participant(s).

Scheduled meetings should be held for the full REC review of a substantive amendment (one that can potential alter the risk-benefit assessment of the project). Amendments that reflect simple or minor administrative changes, or that do not increase the risk to the participant(s) may, at the discretion of the REC, be submitted to expedited review. Notification of the approval of amendments is dealt with in the same way as notification of the approval of original protocols. Non-substantive changes may be acknowledged by a REC letter to the investigator - an example of a non-substantive change being a change in the protocol title.

**ADDITIONAL RESPONSIBILITIES AND DUTIES OF THE REC WHEN REVIEWING RESEARCH PROTOCOLS INVOLVING VULNERABLE POPULATIONS**

Prior to reviewing any protocol involving vulnerable or special populations, there should be at least one member currently serving or specifically co-opted onto the REC that can represent the interests of this particular group. The review of research involving vulnerable individuals and communities is discussed in detail in Chapter 12.
Review of a final study report

in order to conclude the study formally, the investigator should officially notify the REC when a study has been completed. (9) A final study report should be submitted.

The reviewer should confirm that:
- the study is permanently closed to the enrolment of new participants;
- the investigators are no longer continuing, or planning to perform interventions on research participants to gather data about them;
- the investigators are no longer continuing, or planning to gather any private identifiable information about the research participants;
- where applicable, the sponsor or monitor has conducted the official close-out visit and will no longer require access to participant records, or contact with the participants;
- the data analysis is complete, or, if the investigators are continuing or planning to analyse data;
- the data do not contain participant identifiers or a link/code to enable the identification of study participants;
- and the investigators will seek permission for any secondary use or sharing of the research data.

CONCLUSION

The continued protection of prospective and enrolled research participants is dependent upon a careful and thoughtful ethical review of research protocols. This chapter has provided a framework for this process. However, many aspects of the review are discussed in more detail in other chapters, particularly in Part III of this book.

REFERENCES

INTRODUCTION

Safety and adverse event monitoring are activities related to the detection, assessment, documentation, reporting and prevention of adverse effects that arise during a study. The Secretariat is responsible for the initial screening and assessment of the reports and establishing whether they need a review by the full REC, the chairperson, other qualified REC members or experts. (1) These events may or may not be related to the research itself but are reported by participants as having occurred during the study. (2, 3) These adverse effects and events are reported consistently, periodically and timely to the REC. It then becomes the duty of a REC to assess these reports and determine if the study should continue. The purpose of safety monitoring is to protect the physical, emotional and social safety of participants.

All research involving human participants require a certain level of safety monitoring and the method should correlate with the degree of risk to participants and complexity of the study. (4) This includes both clinical drug trials, as well as any other research involving human participants. The REC’s role is to ascertain if a study can continue even after an adverse event has occurred. The assessments should be done timely so that participants are not put at risk. All research studies have an inherent risk attached to them and adverse events inevitably occur.

WHAT EXACTLY SHOULD BE REPORTED TO THE REC

It is critical in every study that researchers stress to their participants the importance of safety and adverse event reporting since they are the ones who will be the ultimate source of this information. Their accurate reporting of the events will allow for easy assessment. A critical question for studies is what adverse events merit reporting to a
REC. The increasing conducting of multi-centre or country studies has complicated the reporting pathways for safety information to both regulators and the RECs. Local investigators, in practice, often report unanalysed events to their respective RECs, including reports from other study sites in multi-centre research with limited information, leading to reporting that is uninformative. This is of great concern and may hinder adequate human participant protection. (5)

The recommendation is that every REC should provide guidance, documented in the standard operating procedures (SOPs), on what reports the different studies should submit. A REC may require different reporting guidelines for clinical trials as opposed to those for observational or social and behavioural studies. Safety and adverse event reporting is generally believed to be a requirement for clinical trials, but it is notable that even studies that are not clinical trials can generate a considerable number of adverse events. Adverse events for such studies include physical, emotional and social harm that befalls participants.

In addition to submitting safety information from the sponsor, studies should submit five main types of safety and adverse event reports to RECs, namely those on or generated by:

- adverse events and unexpected occurrences;
- adverse drug reactions;
- serious adverse events (SAEs);
- data safety and monitoring committees/boards, and
- social harm.

SAFETY MONITORING COMPONENTS (6,7)

Each study, ideally, submits a safety-monitoring plan (SMP), detailing how the study will prevent, mitigate and report safety and adverse events. Some studies could include this section within their protocols, or, in the case of a clinical trial, a separate plan could be submitted. SMPs should contain sufficient information to enable the REC to determine whether the SMP is appropriate for the research being done. The following information, as appropriate to the research being undertaken, should be included.

General

Minimal requirements that should be submitted:

a) data, events and incidences that are likely to happen during the study;
b) how many times the review will be done (it should be clear if the frequency is linked to number of participants enrolled or after particular milestone has been reached in the study), and
c) exactly how the study will send periodic review reports to the REC, sponsor and relevant bodies. (4)
Safety Issues

The information on safety issues should include:

a) How identified incidences and events will be handled that have occurred and might affect the risk category of a study, requiring it to be reassessed by the REC. The steps that the study puts in place of communicating such events and/or amendments need to be outlined clearly (e.g. an amendment to the protocol or an event might occur that moves a study from being a minimal risk study to becoming a high risk study);

b) Steps to be taken for monitoring the risk-benefit assessment of the study;

c) Steps and criteria for unblinding of the random assignments of participants, and

d) Procedures for ‘stopping’ the study. The stopping rules should be based on review of study-related events and incidences. Stopping rules should be study specific and indicators of what will trigger the process of stopping the study should be described. (4)

It is generally recommended that clinical trials report unanticipated problems, which are then classified as SAEs. Such events would include those that do not emerge from the particular site itself.

FORMAT FOR REPORTING

The REC should also have a standard format for the reporting of adverse events. The design of the forms and the reporting formats will depend solely on the needs of the REC. The information that they receive should be adequate and complete enough to make a thorough assessment of the cause of the event. A starting point can be the CIOMS Form 1. (8) The forms should, at least, contain the following information:

- pertinent demographic data relating to the participant;
- details of the event, venue, and time;
- the suspected drug or intervention used;
- the probability, as judged by the PI (if a clinical trial) of a direct causal relationship between the intervention and the event;
- the concomitant drugs or other interventions used, and
- what was done to treat or contain the event, including which tests and interventions were done (for example counselling and the withdrawal of the study product).

These requirements are among some of the most basic to allow for a fair assessment. A REC can ask for more or less information, depending on the study.

TIMELINES FOR REPORTING AND REVIEW

Every REC should set timelines for reporting safety and adverse events, and for putting procedures in place for timely review between meetings. Issues regarding safety and adverse events should be reviewed in a timely manner to enable the investigator adequate time to act in the case of a recommendation by the REC and to ensure the
maximum safety of the participant. For instance, the investigator may not withdraw a study product because the event might have been graded as offering only a low risk, whereas the REC had graded the event as having a higher risk. The REC’s decision then needs to be communicated to the investigator to enable action to be taken in a timely fashion.

**REVIEWING SAFETY INFORMATION**

A REC must have an officially recognised system of reviewing adverse events to whatever extent it possibly can. Most of the time, a REC may have insufficient information regarding that to which the study is privy, but it should nevertheless make reasonable recommendations based on the information to which it does have access. When information is lacking, a REC should not be forced to review incomplete data, as doing so may endanger the participants further. Sometimes a REC can ask consultants at a higher level than itself to review events it might not understand. An example of an internationally recognised clinical adverse events grading system follows.

The US Division of Aids (DAIDS) adopted the following toxicity grades as have been summarised in a table for grading the severity of adverse events. (9) Site clinicians should use the toxicity table (available from the same source) to assign toxicity grades to all adverse events. Any one of the following five toxicity grades can be assigned to an SAE:

1 = Mild  
2 = Moderate  
3 = Severe  
4 = Life-threatening  
5 = Death (9)

Please note that each protocol should develop a relevant toxicity table that is appropriate to the study.

**Causality Assessment**

Causality assessment involves the “evaluation of the likelihood that a particular treatment or research activity is the cause of an observed adverse event”. (10) This assessment is best carried out by specialists who have the requisite training in doing these assessments. (10, 11, 12, 13) If in doubt the REC may form a smaller subcommittee that is dedicated to dealing with adverse events, and which does causality assessments.

**CONCLUSION**

The main challenge to a REC that reviews adverse events is obtaining sufficient information from which enough evidence can be gleaned to ascertain, within reason, the cause of the event. Enhancing the quality of reports improves the ability of RECs to react meaningfully to safety issues that affect those enrolled in the research study.
A REC should be able to review adverse events in a timely manner, in order to protect research subjects adequately.

REFERENCES

On-going Monitoring of Research, Post REC Approval

Okyere Boateng, Paul Ndebele, Dan Mwesiga-Kayongo

Key Message: The monitoring of approved and on-going research by the Research Ethics Committee (REC) is essential. This monitoring can take several forms. Passive monitoring usually involves the review of progress reports and annual re-approval, while active monitoring may include informed consent monitoring and site audits.

INTRODUCTION

Research ethics committees (RECs) have been established to protect the rights and well-being of human research participants, as a response to the historical abuses of human beings in research. (1) Research ethics scandals that have occurred after the RECs had given their initial approval clearly indicate that the initial review of protocols to determine their ethical acceptability does not necessarily provide adequate safeguards for the human participants involved. Even though monitoring processes are deemed necessary and important they are often not adequately implemented, due to various reasons discussed below. It therefore becomes difficult to assume that the research will be conducted as it was originally planned and approved by the REC.

Without approval, investigators cannot proceed with their research. It then stands to reason that, once the necessary permission has been granted, RECs will still be responsible for ensuring that human participants will be adequately protected while the research is being conducted. The monitoring of research is also acknowledged as being the responsibility of other stakeholders, such as the sponsor and other regulatory authorities. This task is usually delegated to monitors, as well as to data safety and monitoring boards, and, on occasion, external auditors. The CIOMS guidelines and the Declaration of Helsinki, which are the main ethical guidelines guiding the ethical conduct of biomedical research internationally, emphasise the importance of the initial ethical review, with relatively less emphasis being placed on the ongoing monitoring of
approved studies. (2,3) Thus, these ethical codes and guidelines have been described as ‘front ends’, because they primarily focus on the REC initial review. Monitoring is a method of evaluating whether or not an approved research proposal was actually implemented according to the written research proposal and approval criteria of the REC, with no deviations. Annual reviews are normally regarded as the lowest level of the monitoring process. Kilama has reported that many RECs in Africa do not often monitor adherence to the approved research protocol. (4) Sometimes these RECs also do not have a system of receiving and reviewing progress reports from ongoing or completed research for various reasons, usually due to limited capacity.

When research poses significant risks to participants, efforts should be made to institute a rigorous system of oversight to protect those concerned. The lessons that have been learned as a result of past abuses of research participants should inform stakeholders of the shared responsibility of ensuring that there is increased vigilance in protecting those who have volunteered to participate in research. RECs have the authority to ensure compliance with the recommendations that they have made concerning protocols that have been given approval. The WHO’s guidance for RECs requires the committees concerned to establish standard operating procedures (SOPs) that describe the process by which they will ensure adherence to the study protocol and compliance with the conditions of approval set out by them. (5) Such a procedure clearly provides the mandate for RECs to observe or to have a third party to observe, both the consent process and the monitoring of research activities.

As was mentioned earlier, there are several different types of monitoring and various stakeholders, including sponsors and other authorities, who are involved in the process of monitoring. The following categories of research oversight by a REC should form an integral part of the processes of a well-functioning REC (6, 7):

- periodic continuing review (which is conducted usually once or twice a year);
- monitoring of the consent process;
- the monitoring of data integrity;
- site visits that are either random or targeted, and
- the requirements for reporting of reportable issues and events (discussed in Chapter 7).

**PERIODIC CONTINUING REVIEW (WHICH IS CONDUCTED USUALLY ONCE OR TWICE A YEAR)**

One method for conducting oversight of an ongoing approved study entails the periodic review of study progress. Most RECs depend on the written reports submitted by investigators to assure them that the studies are being conducted in an ethical manner, and that the approved protocol is being adhered to. In the course of conducting research, investigators might come across new information concerning risks and benefits, or discover a need to alter the study design, or to modify the information and consent documents concerned. There may well be a need to update the information that
was originally submitted to the REC involved. Therefore, continuing review might also involve the review of protocol amendments, changes to the informed consent form and to any other information that is relevant to the conduct of the investigation. Periodic continuing review of research protocols, which is a passive form of monitoring, gives the RECs the opportunity to re-evaluate the risks and benefits for enrolled research participants.

RECs should determine whether or not continuing review is necessary once the data collection is complete, that is during the analysis and reporting phase of the project. In many instances, such ongoing review is not necessary, and the investigators concerned can be advised to submit a final study report once the project has been completed. Continuing review is aimed at safeguarding the safety and well-being of study participants during the time that they are actively participating in the study. If there is an active follow-up component, the associated follow-up activities, including adverse events, require reporting and reviewing. It must be emphasised that, during the continuing review, the REC should not only be concerned about the informed consent and risk assessments, but also about issues that are related to the culture of the study area, the local laws and the taboos that might have been overlooked during the initial review, as well as any reports that are based on third-party observations or that appear in the media.

**ACTIVE MONITORING, INCLUDING SITE VISITS**

In addition to the above, RECs are also expected to conduct active monitoring by way of field visits or site inspections, or through audits that can be either announced or unannounced. (8) Such inspections and audits provide an opportunity to find out whether researchers are conducting the research according to the approved protocol, as well as an opportunity to find out whether participants who have been enrolled in a study understand what the risks, benefits and harms involved are. RECs need to be sure that the participants are aware that what they are involved in is not a form of health care, but that it is research. Site visits are particularly useful for studies involving vulnerable populations, or for research sites or entities that are conducting several projects simultaneously. They are also valuable when higher risk studies are being conducted, or when the research site concerned has a record of reporting higher than expected numbers of protocol deviations and adverse events. It is not uncommon to underestimate the risks of procedures with which one is familiar and therefore researchers might, in the course of their research, underestimate some study-related risks which may only become apparent during the course of the project. Site visits can also be helpful where the REC involved has obtained information about a research study that raises particular concerns.

McNeil et al. reported that, in a survey of 92 researchers, 14% said they had deviated from their own protocols without having obtained approval to do so, by making changes
to the overall study design, the defined subject samples, or the nature of the participation required of the subjects. (9) In situations where investigators tend not to adhere closely to the approved protocol, widening the role of RECs to include the random monitoring of research that they have approved might deter, detect and reduce research ethics irregularities. If protocols involve complex treatment regimens, or require critically timed safety interventions to prevent serious toxic effects, RECs might wish to institute monitoring, in order to ensure that the approved procedures are being followed. (7) The documents to be inspected during inspections/audits, such as in clinical trials, are likely to include informed consent forms, case report forms (CRFs), and severe adverse event (SAE) reports. A major challenge that such inspection might pose is that the monitoring process might influence the behaviour of both the investigator and participant, in relation to a phenomenon that is referred to as the Hawthorne effect. (10) In such cases the investigator would tend to exert extra effort to make the participant understand what the study in which they are participating is about, and the participants, in turn, knowing that their knowledge will be tested by a REC member, are likely to exert additional effort to ‘pass’ the test concerned. (10, 11) In situations where the REC lacks the expertise or resources to conduct site visits, external monitors or other appropriate professionals could be co-opted to serve in such a function.

MONITORING OF INFORMED CONSENT

The REC has the authority to require that the consenting process is observed either by an REC member or a REC delegated third party or monitor. Particularly in greater than minimal risk studies, and in studies involving vulnerable groups, it would be appropriate to execute some form of consent monitoring. A variety of interventions have been suggested, including the third-party assessment of competency, the involvement of a subject advocate in consent negotiations, and direct monitoring by the REC. (11, 12, 13, 14) Robertson has maintained that RECs should monitor the consent process by developing methods for testing participants’ understanding of the research study involved. (15) Remedial action can then be taken when appropriate. Monitoring can also be seen as a means of quality control, whereby the REC observes the consenting process and finds out at first-hand the adequacy of the entire process. Such testing of adequacy can include an initial evaluation of the degree of competence and voluntariness involved, of the clarity of information being conveyed to the potential research participants, and of the participants’ understanding of this information.

ADVERSE EVENT REPORTING AND MONITORING

It is important for RECS to set up requirements for reportable events as a way of monitoring them. The RECs should develop the tools to be deployed, and must specify the scope, the details, and the methods used for such reporting. Reports like the above include:
On-going Monitoring of Research, Post REC Approval

- adverse events reporting;
- protocol deviation reporting;
- unexpected events reporting, and
- the reporting of problems encountered.

Upon receipt of the reports, the REC should review them to learn more about the reason for their occurrence, as well as more about the measures that have been put in place to help ensure that there will be minimal chance of such events recurring in the future.

This topic is covered in greater detail in the previous chapter (Chapter 7).

OTHER ASPECTS

Weijer et al. propose three models for the administration of the research monitoring process. (7) In Model A, the REC monitors the research projects directly, based on what processes have been documented in their SOPs. In this model, which is appropriate for greater than minimal risk studies, monitoring is initiated by the REC concerned. In Model B, the monitoring is investigator-initiated and the investigator requests the REC to conduct an audit. In Model C, the institution may establish an office for research audit that falls under the supervision of the REC, and which works in close affiliation with the REC.

In Africa, where there are often limited resources, poor infrastructure and other challenges to conducting onsite visits, it may be appropriate for RECs to adopt or to use some existing structures to help protect the human participants who are enrolled in research. For example, in a situation where research will be taking place in school-based environments, the REC could liaise with the local department of education, and the school inspectors concerned could be requested to provide some insights regarding the conduct and progress of the study. Similarly, in clinical research, the REC that gave approval for the study could interact with the members of the district health management team, or similar structure. These professionals could be requested to complete a checklist, or to submit an independent written report to the REC regarding the progress of the study. Specifically, an opportunity could be created to explore the perceptions regarding both the strengths and the weaknesses of study implementation. Such reports would obviously need to be treated confidentially. Opinion leaders, and a number of bioethicists, have supported the call for the communities where researchers are conducting studies to become actively involved in it and possibly to come to ‘own’ the research. It is both ethical and feasible for the community to establish and to ‘own’ monitoring structures so as to minimise any threat of exploitation. Suitable community representatives can be organised and trained to provide oversight of community-based research initiatives. Where appropriate, the task can be taken up by the members of existing community advisory boards. (16, 17) Since such boards are community-based, their members could be trained, resourced adequately, and empowered to take on an additional oversight responsibility.
Another alternative strategy is for RECs to ‘network’ their activities and to provide monitoring services in an area close to where they are located. For example, if REC X were to approve a study K that is being carried out at a location close to where REC Y is located, then the latter REC could offer its services to monitor the study, particularly if some form of reciprocal arrangement can be devised. It is essential that RECs remain cognisant of the fact that their primary role is to protect the rights and welfare of all relevant participants who are enrolled in the research falling under its oversight.

CHALLENGES TO THE MONITORING OF APPROVED RESEARCH PROJECTS

Currently, most countries in Africa have now established some sort of system for the ethical review of research proposals. (18, 19, 20, 21, 22) However, these processes are often challenged by the limited resources available, including inadequate human resources and funding, as well as an undersupply of equipment, office space and meeting premises. Thus, a restricted human resource supply, poor communication and the lack of accessibility to project/study sites mean that many RECs find it difficult to undertake active monitoring as has been described above.

Scarce resources (particularly suitably qualified human resources) will definitely limit the smooth running of any oversight system that is established by the REC and this may in turn, place additional stress on the functioning of the REC as a whole. However, irrespective of the fact that research oversight is subject to many challenges, it is the responsibility of the RECs to find effective ways of ensuring that their obligation to protect research participants is adequately fulfilled. In some situations, after the initial approval has been granted, researchers do not spontaneously submit reports for continuing review. Thus, as a minimal monitoring requirement, all RECs should develop a system that enables the REC administration to provide timely reminders to researchers to submit reports for continuing reviews. RECs can also do both for-cause and not-for-cause monitoring, when it is necessary.

CONCLUSION

The active monitoring of approved research by the various stakeholders concerned is essential if the safety and welfare of study participants is to be assured. Responsible stakeholders need to set aside some resources to support monitoring activities. The following practical recommendations related to monitoring require attention:

1. Post-approval monitoring should form part of the protection system of human research participants.
2. RECs need to exert effort in terms of continuous monitoring, including dedicating such resources as the required time and funds.
3. RECs should stipulate reporting requirements in their letters of approval.
4. RECs should develop tools that are necessary for the continuous monitoring of approved research, which they should make available to the researchers concerned.

5. Post-approval monitoring can take other forms than merely relying on the reviewing of annual reports. RECs need to consider using both passive and active monitoring, including conducting site inspections.

6. RECs should be on the lookout for complaints and news reports regarding specific studies, and may need to initiate investigations, where necessary.

7. After any post-approval monitoring activity, there is a need to prepare and to submit a report to investigators, so that they can work on addressing any areas of need.

8. RECS can be innovative in working closely with other stakeholders and organisations in improving the continuous monitoring of approved research.

REFERENCES


PART III

SPECIFIC TOPICS
INTRODUCTION

A major requirement for the ethical conduct of research, involving human subjects, is the informed consent of the potential participant. Potential participants recruited should have adequate knowledge of the study and its implication to them as individuals, before agreeing voluntarily to participate. (1) Informed consent is the practical application of the principle of autonomy and respect for persons, whereby the researcher demonstrates her respect for each research participant as a person, who is capable of decision-making. (2) Two ethical obligations are required, namely:

a) Respect for the autonomy of individuals: Such individuals should be allowed the opportunity to choose whether to participate in a study or not.

b) Additional protective measures for vulnerable persons with limited autonomy.

The WHO standards and operational guidance for research ethics committees (RECs) guide RECs to examine both the research information provided, as well as the informed consent process. (3) There are challenges and controversies that may arise during the informed consent process, especially in developing countries that are characterised by poverty, low literacy levels, limited access to health care and other negative factors. Informed consent is especially complex when a language or cultural barrier, or both, exists between researcher and participant, as well as when the participant’s views and beliefs regarding disease causation differs from those of the researchers. (4) Cultural perceptions of personhood also influence the decision-making process. In certain cultures (e.g. Western culture) persons will often make decisions independently. However, in an African context decision-making is often communitarian, involving
consultations with family/community members. (5) The communitarian consent process requires communal decision-making through consensus. In the communitarian system, members create a forum (imbizo) to discuss the issues at stake. The elders of the community usually preside at this forum and all viewpoints are shared, where after the elders, based on the prevailing opinion of the group, will communicate a summary. (6) According to Mkhize, the decisions and knowledge are constructed socially and communally through negotiation. The informed consent process in African societies may be a semiotic process, involving various stakeholders, who should be involved in negotiating the informed consent process in their cultural community. In order to ensure meaningful informed consent, researchers have to understand the cultures and beliefs of the communities from which they recruit research participants. This section addresses the unique and peculiar issues raised by the process of informed consent in the African context.

What informed consent is

The Declaration of Helsinki states that each potential participant must be adequately informed of the study aims, methods, potential risks and anticipated benefits accordingly. (6) The Declaration also states that individuals should be assured of the right to withdraw consent to potential participation at any time during the research process and emphasises that researchers should obtain the potential participant's voluntarily given informed consent, preferably in writing. (7) Consent consists of three parts: i. the researcher provides adequate information about the proposed study; ii. the prospective participant understands the information that is being provided, and iii. the prospective participant makes a decision based on information provided on whether or not to join the study. (8)

Informed consent process

Informed consent means more than simply obtaining the signature of the research participant. It is a process that involves conveying accurate and relevant information about the study, its purpose, potential benefits, known risks, alternatives and procedures, in a language which the participant best understands. It also involves answering questions and enabling the potential participant to make an informed decision whether or not to participate in a given research study. The informed consent process should be culturally sensitive and locally appropriate. (9)

The medium and context in which information is conveyed is fundamentally important. The ability of the potential participants to understand is linked to their intelligence, as well as their individual maturity, rationality, and language. It is important to determine true understanding, through some form of oral or written comprehension tests. There should be special provisions for participants whose comprehension abilities are limited. In such instances researchers are obliged to seek permission from their legal guardians or family members (see below). (9) These chosen guardians or family members should
have a close emotional tie with the incompetent person, be knowledgeable about their situation and most especially have their best interests at heart.

**Decision-making capacity**

Only individuals who are legally classified as adults of sound mind can give consent. There are, however, exceptions where minors may consent after being declared emancipated and competent by higher legal authority. Consent must be free of coercion or undue influence. Coercion occurs when one person intentionally uses threat of harm to achieve compliance in another. However, subtle manipulation or persuasion may be far more common. This manipulation of a participant’s choice can occur through the controlling influence of a close relative or by the perceived (or real) threat of withdrawal or limitation of access to health services that the individual regards as valuable. Undue influence is the scenario where an excessive, unwarranted, and/or inappropriate reward is offered to potential participants for their agreement to participate.

**Requirements of informed consent**

For consent to be valid, the researcher must:

a) Provide all the information necessary for adequate informed consent.

b) Allow the prospective subject full opportunity to ask questions.

c) Ensure that all unjustified deception, undue influence or intimidation are excluded.

d) The prospective participant must have adequate knowledge of the relevant facts, as well as the potential consequences of participation, with sufficient opportunity to consider whether to participate, before consent is sought.

e) The consent should, where possible, be written consent, as documented evidence of the process. However, in appropriate circumstances verbal consent can be obtained, but should be adequately documented with a witness (preferably two witnesses) present to confirm the validity of the process. The witnesses should not be members of the research team.

**Vulnerable participants and informed consent**

Vulnerable groups are made up of individuals who cannot represent or defend their own interests (see chapters 12 and 13). Where a study is dealing with any vulnerable populations or individuals from these groups, the researchers have to make certain that they take appropriate steps to ensure that harm to these individuals is minimised and that the individuals are not placed in a worse-off situation by virtue of their research participation. Obtaining informed consent from individuals from the following groups requires special considerations and can be challenging:

a) Children;

b) Patients with mental health problems, including all forms of dementia and learning disabilities;
c) Individuals engaging in illegal behaviours or individuals with stigmatizing conditions (Commercial sex workers, homosexual men, drug addicts);
d) Seriously ill patients, and
e) Convenient, captive and hierarchical populations (soldiers, prisoners and students).

Children

The principles of informed consent discussed earlier apply as much to studies with children as those involving adults, although taking into account that children may not be able to legally consent on their own. In addition to obtaining consent from the child’s guardian, where possible the child’s willingness to participate or co-operate (assent) must always be obtained (see chapter 13).

Individuals with learning disability

People with learning disabilities should never be invited to participate in research that can be done equally well with volunteers or patients who are able to give informed consent. Many individuals, depending on their degree of learning disability, will be able to give consent on their own behalf. Researchers may however encounter difficulties in ensuring the consent is informed, hence more skills and patience are required in such research contexts.

Individuals with mental health disorders and dementia

As with other vulnerable groups, research with individuals with serious psychiatric problems should only be carried out if it is specifically aimed at benefiting the patient and if it cannot be done on otherwise healthy adults. The difficulty with obtaining informed consent from this category of individuals is that, their full understanding of the purpose of the study may influence the behaviour or attitudes, which the study is seeking to measure. Hence the researcher may request permission to not reveal all relevant information about the study to the participants upfront. RECs need to consider the potential risk-benefit equation of such studies very carefully before providing approval and ensure that there is potential benefit for the class of participants.

Populations engaging in Illegal behaviours or individuals with stigmatising conditions

In some countries the following categories, are regarded as engaging in illegal behaviours; commercial sex workers, intravenous drug users and men who have sex with men. These behaviours are considered illegal as the law in certain countries prohibits such activity. Getting consent from individuals engaging in such behaviours thus becomes difficult, as they are often already stigmatised and reluctant to sign consent documents. This is one context where verbal consent may well be ethically more acceptable than written consent as there would therefore be no way of directly linking the research participant to the study. Stigmatising conditions do vary depending on the society or
local community. Stigma may also result from beliefs or incomplete knowledge about certain conditions such as albinism.

**Convenient, captive and hierarchical populations**

Populations that are convenient include those who are readily available such as students. There are other groups who may be both readily available and ‘captive’. These include prisoners, military personnel and institutionalised personnel. It is often challenging to obtain genuine informed consent from this category of persons as they may feel coerced or manipulated to participate in a research study by virtue of their dependant status on others. Those in hierarchical setups may be instructed by their seniors to participate in research.

**CONCLUSION**

Informed consent is a requirement for the ethical conduct of research. African RECs can play an important role in improving informed consent by ensuring informed consent is meaningful. The following practical recommendations need consideration:

1. Researchers should clearly discuss the processes they will follow in accessing individuals and obtaining individual informed consent.
2. Researchers should also clearly discuss how they will deal with gatekeepers and significant others, in the process of obtaining informed consent.
3. The informed consent documents are prepared in non-technical language and are translated into the local language.
4. Appropriately trained and qualified members of the research team, who preferably are familiar with the local language, should be delegated the task of obtaining informed consent.
5. The consent processes are culturally and locally appropriate.
6. The incentives offered are not ‘undue’ and that there is no coercion or persuasion implied in the informed consent documents or present in the environment in which the study will take place.
7. The researchers have included some processes for assessing understanding of the disclosed information.
8. The REC makes use of the opportunity to talk to study participants during site inspections to find out how they have been recruited into the study, as well as their understanding of the disclosed information.

**REFERENCES**


INTRODUCTION

Risk-benefit assessment is a crucial aspect of ethics review to ensure the safety of human participants and should be done in a systematic way prior to ethical approval. (1, 2, 3) The risk-benefit analysis should be favourable with a reasonable relationship between risks to the research participants and the anticipated benefits (if any) and/or the importance of the potential knowledge gained. (4, 5) There are major debates about when risks are reasonable in their relationship to potential benefits and critique is often that RECs are not consistent in risk assessment. (6) For this reason it is important to use a robust systematic approach to risk-benefit assessment.

Important definitions (2)

Risks: Risk can involve physical, psychological, social or economic harm as a result of participation in research, and can vary from minimal to severe: (4, 7)

Physical risks: These risks include any bodily harm, ranging from minor or serious harm that may be temporary or permanent. The risks may also occur immediately or be delayed.

Psychological risks: The participant may suffer emotional discomfort or anxiety, develop a sense of shame or a negative perception of self, or develop thought and behavioural aberrations.

Social risks: The participant may be exposed to discrimination or to social stigmatisation in the workplace or in social life. (For example a research participant applies for health
insurance after participation in an HIV vaccine trial, but is penalised because he/she now has antibodies for HIV and tests positive.)

Economic risks: The participant incurs direct or indirect financial costs due to participation in the research project.

Risks are generally classified into the four categories outlined in the following table (4):

<table>
<thead>
<tr>
<th>Category of risk</th>
<th>Likelihood of occurrence of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research that involves no more than minimal risk.</td>
<td>Magnitude and probability is not greater than the risks that a participant may experience in daily life in a stable society, or during routine physical or psychological investigations or tests.</td>
</tr>
<tr>
<td>Research that involves more than minimal risk, but with the prospect of direct benefit.</td>
<td>The potential risk is justified by the anticipated benefit that the research participant may gain from participating in the research; the benefit should be at least as favourable as the benefit resulting from the use of any alternative method or approach.</td>
</tr>
<tr>
<td>Research that involves more than minimal risk, with no prospect of direct benefit, but which is likely to yield important generalisable knowledge regarding a disorder or condition.</td>
<td>The risk represents only a minor increase over minimal risk, and is reasonable in relation to the participant’s actual medical, dental, psychological, social, or educational situation. The intervention or procedure is likely to yield generalisable knowledge regarding a disorder or condition that is of vital importance for the understanding or amelioration of the participant’s disorder or condition. There should be adequate provisions for obtaining children’s assent, as well as parental/guardian consent.</td>
</tr>
<tr>
<td>Other research</td>
<td>The REC may approve research that does not fall into one of above three categories only if the research will potentially assist in understanding, preventing, or alleviating a serious health care problem affecting the particular community or population. Additional external expert opinion in the particular field of research is generally necessary to assist the REC in its deliberations.</td>
</tr>
</tbody>
</table>

The REC member should consider the following issues in risk assessment:
- Is the target group or population's participation justified?
- Is the target group or population a vulnerable population and if so, is it absolute necessary for them to participate to answer the research question? Are adequate protective measures being taken to ensure risks are minimised?
- If the research involves children, is their participation essential to answer the research question? Has the research previously been undertaken in adults and do the results of the adult research indicate that children will benefit from the research, or will it at least not be harmful to the child participants? Will the parent be present during the research intervention to support the child emotionally? Will it be possible for the parent to terminate the child’s participation at any time during the research? If certain research procedures (e.g. those involving sensitive personal matters, or the physical examination of adolescents) require that the parent not be present during
the research, has the investigator motivated the absence of the parent during the course of the study in the research protocol?

- Have the investigators taken into account the participant’s previous experience of illness and medical interventions?
- What method did the investigator use to determine the number of participants to be enrolled for the study, and is the number justified (keeping in mind that the sample size should involve the critical number of participants necessary to obtain statistically significant and valid results)?
- Are the proposed interventions the least invasive (both physically and psychologically) that can be used to obtain the information required for the study?
- Have the investigators described in detail how the assent/consent should be obtained?

For research involving medical interventions, all previous research including animal research should be considered. The relevant literature regarding animal studies should be available, and the investigator should indicate whether the animal research is complete.

Benefits: Benefits refer to the potential benefit that research participants may experience as a result of their participation. In health care research this ranges from potential cure or improvement of the underlying illness, to general improvement in the individual’s well-being. The answer to the research question should be the desired outcome and should be advantageous to the participant. (1, 2, 7) Ancillary services provided during participation in health care research, and which are not directly linked to the study objectives, cannot be classified as benefits during the risk-benefit assessment process.

**APPROACHES TO RISK-BENEFIT ANALYSES**

Risk-benefit assessment is a challenging and complex process, since the assessment is for potential risks and anticipated benefits as the true risks and benefits can only be known after completion of the research. (8) Coleman and Bouesseau note that this assessment involves not only the evaluation of scientific arguments but also value judgements that can be significantly influenced by personal opinion and bias. (9) The predominant approach to risk-benefit assessment of health care research for the past decade has been ‘component analysis’, developed by Weijer (8, 10), or the ‘net risks test’, proposed by Wendler and Miller. (11) The two approaches are both “procedure-level risk-benefit assessments”, which focus on assessing the risk-benefit profile of individual study procedures, rather than undertaking a global risk-benefit profile of the entire study. Whereas these approaches were developed with clinical trials in mind, they can, nevertheless, be equally applied to other categories of clinical/medical research, each of which shall be briefly discussed.
Component analysis (8, 10)

The component analysis approach is based on the premise that clinical research involves a mixture of ‘therapeutic’ and ‘non-therapeutic’ interventions and procedures. A risk-benefit assessment of the interventions should, therefore, be guided by different moral considerations. Therapeutic interventions are those interventions that are administered to the research participant with the intention of having a therapeutic effect, and where there is a strong possibility of potential benefit to the research participant. Non-therapeutic procedures or interventions have no therapeutic effect, or present no prospect of direct benefits to the research participants.

A key concept in component analysis is the requirement of a state of ‘clinical equipoise’ for all novel therapeutic interventions. Clinical equipoise means that there is a genuine uncertainty among experts in the field as to what is the best therapy for any particular disease or health condition. (10) Based on such an approach, REC risk-benefit analysis must begin with a separation of the various study procedures and interventions into either ‘therapeutic’ or ‘non-therapeutic’.

For the therapeutic procedures, the risk-benefit assessment should pass the ethical standard of clinical equipoise, and should be consistent with the requirements of competent clinical care. Sufficient existing evidence (such as results from animal studies) should be in available to support the expectation of potential benefit. The REC should, after carefully reviewing the justification for the study and the existing literature on the issue, consult with independent clinical experts, where necessary. For a therapeutic procedure to be deemed ethical by the REC, the risks that are posed to the research participant must be considered acceptable within the context of the anticipated benefits.

For non-therapeutic procedures, the risks associated with the procedures should be reduced to the maximum extent allowed by a valid study design, and should also be considered acceptable within the context of expected new knowledge generated from the study. Thus, the REC must assess whether the risks have been reduced to the maximum extent possible. If not, the REC should investigate alternative reliable procedures that are in line with the proposed scientific study design. For instance, RECs may suggest alternative venues for an interview if they find the proposed venue to be problematic, or they may recommend a verbal informed consent process, rather than a written one. The REC may even suggest alternative procedures, or consult independent domain experts and community members, to assist in determining whether the risks involved are reasonable for the scientific study design or the local context. (5)

Weijer and Miller propose that the REC should decide whether the project represents ‘minimal risk’ or ‘minor increase over minimal risk’ when such vulnerable populations as children and intellectually challenged participants are involved. Minimal risk is described as those risks that are ordinarily encountered in daily life within a stable society. (5) This assessment can be challenging and debatable, since there are various
interpretations, particularly in an African context, where the conditions encountered in everyday life are harsh, and the experience of a stable society may be limited.

After the above-mentioned deliberation, the REC can then proceed to decide whether or not to approve the study. The key issue is whether the sum and balance of risks is acceptable in relation to the anticipated benefits that are likely to be obtained from the study.

Net risks test (11)

Wendler and Miller devised the net risks test as an alternative method of risk analysis. (11) They hold that the concepts 'therapeutic' and 'non-therapeutic' are not always clear, and that they may even be unnecessary.

According to these authors the proposed process for RECs to follow when conducting a risk-benefit assessment is as follows:

**Step 1:** Identify all study interventions and procedures, and conduct a risk-benefit (burden) assessment of each one. \((A = \text{favourable or unfavourable})\)

**Step 2:** For each study procedure or intervention, identify an alternative, such as what would happen if the participant were to be managed or treated as per the usual standard of care, and also assess the ratio of risk (or burden to benefit). \((B = \text{favourable or unfavourable})\)

**Step 3:** Compare A to B for each procedure or intervention.

**Step 4:** If the risk-benefit profile of the research interventions (when added together) is assessed as being equivalent to the alternative, no ‘net risks’ are involved. However, if the risk-benefit profile of the research interventions is assessed as being worse than the alternative would be, then ‘net risks’ are involved.

**Step 5:** If the net risks of the research intervention are not excessive OR if they are considered to be justified by the new knowledge that is likely to be gained by undertaking the study, then the REC can approve the study, even if the net risks of the alternatives are lower than those of the proposed study. Interpreting the concept of ‘excessive risk’ may be quite challenging, but it generally means that there is no evidence that the proposed intervention could result in serious or permanent disability, or death. Finally, in assessing ‘net risk’, the REC must be aware of the cumulative risk. Thus, for example, while one or two blood draws may be considered to be of negligible risk, serial blood draws over many weeks or even months may, in fact, constitute a considerable burden.

The terms ‘risks’ and ‘burdens’ are often used interchangeably in the context of risk-benefit discussions, although they are not completely synonymous. Whereas ‘risk’ means the potential for some form of harm occurring during the research process,
‘burden’ can incorporate risk, but it also refers to such inconveniences as the amount of time spent, or the recurrent exposure to painful procedures (such as blood draws). Although the above model focuses specifically on risk assessment, it is also useful to incorporate an assessment of overall burden into the final ‘net risk’ calculation.

An example of how the process above could be applied to a specific study is illustrated in the table below. A clinical trial involves a new anti-diabetic agent with the potential to reduce organ damage caused by diabetes significantly. The REC may decide that although the study does present a moderate increased risk over the alternative options, the potential for new knowledge and possible benefit to both participants and future diabetic suffers means that the study can be approved.

**Table 2: Application of a net risks test to a specific study**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Risk/Burden-Benefit Assessment</th>
<th>Standard Of Care</th>
<th>Risk/Burden-Benefit Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational drug for six months</td>
<td>Some unknown risk negative</td>
<td>Registered drug for six months</td>
<td>Known risks - neutral</td>
</tr>
<tr>
<td>Blood draws every two weeks for six months</td>
<td>Significant additional burden</td>
<td>Blood draw once in six months</td>
<td>Minimal burden</td>
</tr>
<tr>
<td>MRI scan of abdomen</td>
<td>Minimal additional burden</td>
<td>No magnetic resonance imaging (MRI) scan required</td>
<td>No burden</td>
</tr>
<tr>
<td>Net overall risk/burden</td>
<td>Moderate</td>
<td>Net risk/burden</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

While the two risk-benefit assessment methods discussed above may differ in their approach, Westra and De Beaufort suggest that integrating them in what they describe as a ‘procedural-level risk-benefit assessment’ may actually increase the effectiveness of the risk-benefit assessment. (11) According to their perspective, risk-benefit analysis should involve two important phases, namely a practical phase where the potential risks are identified and the normative phase where the acceptability of the risks are assessed.

Rajczi proposes a somewhat different approach to risk-benefit analysis then the component approach described. He suggests that the standard that the IRB should use before deciding whether or not to approve a research proposal is the reasonable person standard. Thus if a hypothetical rational, well-informed, self-interested and competent person (such as an REC member) would agree to be a participant in this study, then the risk is acceptable. This principle is called “the agreement principle” and the approach is compatible as an adjunct to the methods described above. In essence, if REC members would be reluctant to take part in a study themselves, or allow their children or parents to participate (assuming hypothetically that the study is relevant to them) then they should not approve the study. (12)
CONCLUSION

Risk-benefit assessment should be contextualised, taking into consideration the sociocultural, economic and political context in which the research is undertaken. In this regard, the anticipated benefits with respect to the potential risks of undertaking research into diabetes and associated factors may be more favourable in community A, with a diabetes prevalence of 30%, than in community B, with a prevalence of 4%. Moreover, the potential risks of participating in research on a ‘controversial’ topic, say homosexuality or abortion, may be higher in a country where such practices are illegal than in countries where the practices are legal, as participation in such a study may actually endanger the well-being of the participant.

It is also important to ensure that the additional protection that is required by such vulnerable populations as pregnant women, children, the elderly, and prisoners are adhered to in the risk-benefit assessment. (5) Traditionally, only “minor increase over minimal risk” is allowed for research involving children (see Chapter 12). The situation is especially difficult to assess if there are non-therapeutic procedures that must be similar to the criterion of risks expected in ‘normal daily life’, but controversy remains as to whether such risks pertain to healthy or sick children.

The REC should conclude by ensuring that there is a reasonable relationship between the potential risks and the anticipated benefits for both therapeutic and non-therapeutic procedures.

REFERENCES


**Suggestion for further reading**

WHAT IS A CLINICAL TRIAL?

A clinical trial is a prospective research study that is aimed at testing the effectiveness of a new intervention, usually by comparing it to another established treatment or to no treatment (a placebo). The ‘intervention’ can be a drug, a medical device, a surgical procedure or any other therapy aimed at improving health in some way. (1) When we discuss ‘clinical trials’, we often mean clinical drug trials, but it is important to note that many therapeutic interventions which are not drugs can be tested in a clinical trial. Most clinical trials have two or more ‘arms’ (‘multiple-arm’ studies), but a clinical trial can also have one arm (‘single-arm’ study). Study participants are usually randomly allocated to a particular ‘arm’ of the study (randomisation). All participants in the same study ‘arm’ of a clinical trial will receive exactly the same treatment. A double-blind study means that neither the study investigator, nor the study participant knows which drug or intervention the participant is receiving. In contrast, a single-blind study usually means that the study investigator knows in which study arm the participant is placed, but the participant does not. For example, a double-blind randomised clinical trial to test a new malaria vaccine against a placebo means that study participants will be randomly allocated (by means of tossing a coin, for example) to receive either the active vaccine or a non-active substance that is made to look identical to the vaccine (placebo). Neither the investigator nor the participants knows whether a particular
participant will receive the active vaccine or the placebo. An open-label clinical trial means that both the study doctor and the participants know exactly which drug is being administered and what effect it is likely to have on the participant.

Clinical drug trials: Phase I-IV

Clinical drug trials are trials that are specifically aimed at developing new drugs for the treatment or the prevention of illness. The process of developing a new drug is a very long and difficult one, which usually starts with laboratory and animal testing. The early studies conducted, usually in animal models, produce ‘preclinical data’. Once sufficient preclinical data have been accumulated, the drug developer (usually a pharmaceutical company) will move on to the different clinical phases of drug development:

**Phase I:** These studies are the very first steps taken in testing a new drug on human participants. Those who are enrolled for them are usually healthy volunteers who are often paid to participate in the studies because they can derive no benefit from the study and because there are often unforeseeable risks involved. The main purpose of such studies is to provide initial data on the safety and pharmacokinetic profile of the drug (in terms of how the drug reacts in the human system).

**Phase II:** After the successful completion of Phase I studies, the drug developer moves on to Phase II studies, and enrolls participants who are suffering from the disease for which the drug is intended. The aims of Phase II studies would be to establish additional short-term safety data, establish associated therapeutic data, and to determine the appropriate dose. Thus, Phase II studies are also often called ‘dose-finding’ studies. These studies are usually short and enrol a limited number of participants (typically 30 to 40, sometimes more and sometimes less). They could be single-arm, multiple-arm, randomised, double-blind or open-label, to name a few examples.

**Phase III:** Phase III clinical trials are undertaken to determine whether or not a drug will eventually be registered as a new drug and marketed. The studies are done on large groups of human participants who suffer from the illness that the drug is intended for. Such studies must be designed very carefully to ensure they can provide statistically sound data that will support the registration and marketing of the new drug. These studies are almost always conducted in several different countries and across multiple sites. They are aimed at establishing the efficacy of the new drug (to determine whether or not it works), as well as at establishing short- and long-term safety data.

Once a drug has been marketed, it can still be employed in additional Phase III clinical trials if there is potential for using the drug for a new condition, for delivering it via a new method of delivery (as a nasal spray instead of as a pill, for example), for using...

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1. The TGN1412 study is a very good example of a Phase I study that went very wrong. All six participants were admitted to intensive care and suffered extensively, and over a long period of time, as a direct result of the study. (16)
it with a new group of patients (with both children and adults, for instance), or for administering a new dose.

All Phase I, II or III studies must be approved by a national drug regulatory authority (NDRA), prior to the start of the study. If no such authority exists in a particular country, the country and REC concerned must ensure that the drug has been approved for trial by a recognised regulatory authority such as the Federal Drug Authority (FDA) or the European Medicines Agency (EMA).

Phase IV: Once a drug has been successfully marketed the sponsor may wish to gather additional information about the drug. An example would be to explore emerging side-effects further. Phase IV studies are, in fact, often not actual clinical trials but, rather, post-marketing surveys.

CLINICAL TRIALS IN AFRICA

This section, which briefly discusses the past, the present and the possible future of the review and the regulation of clinical trials in Africa, includes a brief discussion of national drug regulatory authorities (NDRAs), as well as of RECs. It is important for REC members who review clinical drug trials also to have some knowledge and understanding of the standards and operation of both national and international drug regulatory authorities. However, an in-depth discussion of the latter topic is beyond the scope of this chapter.

Many clinical trials are now conducted in Africa and in developing countries elsewhere in the world, partly because the burden of disease is highest in such countries. (3, 4) Of the almost 100,000 clinical trials conducted annually worldwide, about 10% (10,000) occur in developing countries, including those in Africa. (5) Research conducted in developing world contexts, including the Africa context, where poverty is endemic and where most research populations are ‘considered vulnerable’, means that adequate mechanisms for both scientific and ethics review and for oversight of this research are essential. (6)

Regulation of clinical trials by national drug regulatory authorities in Africa

The World Health Organization (WHO) has noted that the scientific review and approval of clinical trials by a drug regulatory authority should be essential for both drug-producing countries, as well as developing countries, where clinical trials are conducted. These developing countries should develop local expertise that can critically review, regulate and monitor drug research. (7) Changes in the regulatory framework of both Western and African countries now mean that often a drug that is particularly relevant to an African population may need to be reviewed and approved by a local
drug regulatory authority prior to the drug being licensed in Western countries, such as the USA or in the nations of Europe, particularly if the drug is not primarily intended to be used in the latter group of countries. (8)

A regional approach to the regulation of clinical trials has been proposed by the Africa Vaccine Regulatory Forum (AVAREF) of the WHO. (7) The adoption of such an approach would entail establishing a mechanism that allows countries that are in close proximity geographically to pool their resources and expertise in the support of ‘in-country’ NDRAs, thus enabling them to support one another and to conduct regional cross-border reviews.

**RISK-BENEFIT ASSESSMENT OF A CLINICAL TRIAL**

All clinical trials carry the potential risk of harm to participants as well as potential benefits. Such potential exists both at an individual level and at the level of generations of patients to come, who will suffer from the same illness. Evaluating the balance of risk of harm and the potential for benefit is an essential part of the evaluation that takes place in a clinical trial. Generally, the higher the potential for individual risk of harm is, the higher the potential for individual benefit should be.

Risk-benefit assessment is discussed in detail in Chapter 11.

**PLACEBO-CONTROLLED TRIALS**

Placebo controlled trials (PCTs) often present RECs with a challenge. They are almost always considered to offer higher than minimal risk and often, in fact, involve studies where proven treatment already exists. In Africa, specifically in contexts where the participants are vulnerable, have a limited understanding of the biomedical model of disease, and exhibit poor literacy levels, particular care must be taken by RECs to protect the participants in clinical trials adequately.

The Declaration of Helsinki of 2008 states the following:

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
   - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
   - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.

Extreme care must be taken to avoid abuse of this option. (9)
In reality, clinical trials that fall into the latter category are presented to RECs for review and approval on a regular basis by sponsors. PCTs for such conditions as diabetes, hypertension and chronic obstructive airways disease (COAD) involve diseases where standard treatment already exists, but where arguments are presented (by sponsors) to justify the use of a placebo. These arguments, as explained by Miller, centre on the widely accepted notion that a randomised double-blind placebo-controlled study (in which the new drug is tested against a substance that is known to be inactive) is the most scientifically accurate way of testing ‘efficacy’ (whether a new drug is effective). (10) The sponsors argue that drug regulatory authorities such as the Federal Drug Administration (FDA) in the United States prefer clinical trial data that proves the superiority of a drug to a placebo, rather than equivalence with an active comparator. Equivalence studies are regarded as being scientifically suboptimal, with recognised methodological challenges. Also, statistically, they usually require far more participants than do placebo-controlled studies. Due to placebo-controlled studies requiring far fewer participants, they tend to cost much less than equivalence studies, meaning, positively speaking, that fewer participants are exposed to the effects of a test drug. (10) However, RECs must remain cognisant of the fact that scientific justification, even if it is valid, cannot outweigh unacceptable ethical considerations. Miller provides a useful five-point ethical framework for assessing PCTs (see Table 1 below).

Table 1: Ethical framework for placebo-controlled trials (10) p. 266

<table>
<thead>
<tr>
<th>Methodological rationale</th>
<th>Is the study scientifically sound? Is it directly relevant to the participants who will be enrolled for the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair selection of participants</td>
<td>Is the study population particularly vulnerable?</td>
</tr>
<tr>
<td>Assessment of risk, specifically for the placebo group</td>
<td>What does comparing the study risks for those in the placebo arm with those in the other study arms show?</td>
</tr>
<tr>
<td>Safeguards to minimise risk</td>
<td>What safeguards can be implemented to reduce risk?</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Is true informed consent obtainable? How will the informed consent processes be monitored or validated?</td>
</tr>
</tbody>
</table>

A ‘traffic light’ approach to placebo-controlled trials
PCTs can generally be categorised into three distinct risk categories: ‘green’, ‘orange’ and ‘red’ as per the table below, which explains this approach.
### Table 2: Risk categories of placebo-controlled trials

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Features of the category</th>
<th>REC decision-making</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green (low risk)</td>
<td>No proven treatment exists for the disease under investigation; OR</td>
<td>Approve if all other aspects of the study are in order.</td>
</tr>
<tr>
<td></td>
<td>The test drug or placebo will be added on to acceptable baseline therapy (in terms of a recognised standard of care).</td>
<td></td>
</tr>
<tr>
<td>Orange (increased risk)</td>
<td>An established treatment exists for the disease (e.g. diabetes), but a scientific justification is being used to justify the use of a placebo; OR When a ‘green’ study is to be done on vulnerable or educationally/economically disadvantaged participants, it is deemed to be an ‘orange’ study.</td>
<td>Carefully review these studies, using the framework outlined in Table 1. Consider obtaining a report from an additional external expert reviewer prior to the REC meeting. If necessary, co-opt an expert onto the REC for this particular study. Refer to relevant guidelines if available (e.g. treatment guidelines to establish norms for the standard of care for the condition to be investigated).</td>
</tr>
<tr>
<td>Red (high risk)</td>
<td>Participants are to be withdrawn from their usual medication in order to participate in the study, or there is an extended washout period with the chance of a placebo and no background treatment is provided. The study falls outside the scope of applicable drug development guidelines or those for recognised treatment. The study involves a sham intervention (e.g. sham surgery with the use of a local/general anaesthetic). The study involves patients with psychiatric disorders (e.g. bipolar disorder or schizophrenia). When an ‘orange flag study’ involves a particularly vulnerable or an educationally or economically disadvantaged group, it is regarded as a red flag study.</td>
<td>Take extra special care when reviewing such studies, allocating extra time for discussion. Obtain an external expert opinion prior to the meeting. Invite the applicant to attend the meeting and to answer relevant questions. Use Miller’s framework to guide the decision-making. If the study is approved, consider REC monitoring of the consent process, as well as site visits. The REC must be able to justify the approval specifically and to reject such studies, if such rejection is warranted.</td>
</tr>
</tbody>
</table>

**INFORMED CONSENT**

Lema *et al.* report that the informed consent in sub-Saharan Africa is not necessarily always ‘truly informed’ or ‘truly voluntary’, which may be due to socio-economic and cultural factors. (11) Hence, clinical trial participants may, even after having completed the informed consent process, have a limited understanding of the study due to a combination of such factors as language barriers and a non-biological understanding of illness and disease. (11) Informed consent is discussed in greater detail in chapter 10.
THE ‘THERAPEUTIC MISCONCEPTION’

The ‘therapeutic misconception’ has been reported in clinical trials in sub-Saharan Africa and was first described by Appelbaum in 1982. (12,13) The misconception occurs when research participants conflate or confuse research with routine health care. (13) In terms of such a misconception, the participants misunderstand or pay insufficient attention to the disclosures that are made during the research consenting process, and enrol in a research study hoping somehow to gain personally from the study. Both clinical trial participants and clinical researchers, especially those who are also clinicians, can easily lose sight of the difference between a research context and a therapeutic care context. Thus the therapeutic misconception is particularly likely to occur in situations where the person enrolling participants for a clinical trial is also the participant’s usual health care provider, resulting in the participants trusting that the study physician will only act in their best interest. Clinical trials are aimed at producing new knowledge. Often, especially when there is a placebo arm, the individual interests of participants come secondary to fulfilling the aims of the study. ‘Therapeutic misconception’ may well compromise the process of obtaining informed voluntary consent. Lema advocates for the need to undertake empirical research into the prevalence and effects of therapeutic misconception in Africa. (12) Researchers and RECs in sub-Saharan Africa should be particularly aware of this important issue, and they should take the necessary steps to ensure that the effect of the therapeutic misconception is minimised. An essential component of the above is to ensure that the informed consent process is valid. This may mean that, in certain contexts, the responsibility for obtaining or validating informed consent must be delegated to a third party who is appropriately and adequately trained to fulfil such a task, but who is neither the prospective participant’s clinician, nor an investigator in the study.

GOOD CLINICAL PRACTICE, INTERNATIONAL NORMS AND STANDARDS FOR CTS

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline (E6) on Good Clinical Practice (GCP) is an international quality standard that is set for clinical trials. The Guideline covers the standards that have been set for the design, conduct, monitoring, termination, auditing, analysis, reporting, and documentation of such trials. The ICH-GCP aims to ensure that the studies are scientifically and “ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented”. (14)

It is important that researchers comply with the international standards provided by GCP, because such standards have their origins in the fundamental principles safeguarding the rights and interests of participants, as articulated in the Declaration of Helsinki. (9)
Another important reason why the adherence to GCP is essential is to ensure that the clinical data that are obtained from multiple research sites are valid and can be used for regulatory and licensing purposes. REC members reviewing clinical trials must not only familiarise themselves with international GCP requirements, but they should also attend GCP training, particularly if they are regularly involved with reviewing clinical trials. A detailed discussion of GCP is beyond the scope of this chapter. Readers should rather obtain and refer to ICH or similar GCP guidelines. South Africa has published its own set of GCP guidelines that comply with the requirements of ICH-GCP but that also take into consideration issues that are particularly relevant to Africa and to a developing world context. (2)

CONCLUSION

The reviewing and approval of clinical trials is of the most important and the most challenging work that RECs are called upon to undertake. The work is a huge responsibility, especially where vulnerable, economically and educationally disadvantaged research participants are involved. However, the burden of disease in Africa and in other developing regions is very great, and clinical trials are needed to develop new and effective treatments and vaccines for such diseases as malaria, tuberculosis, HIV/AIDS, diabetes, and chronic heart disease, among others. Thus RECs are obligated to take up the challenge of diligently reviewing and appropriately approving such clinical trials. RECs must strike a balance between not creating unnecessary obstacles to the research process on the one hand, and, on the other, ensuring the adequate protection of human research participants. Well-run ethical clinical trials can provide solutions to uniquely African health care problems, build local health care capacity, provide employment, and provide access to improved health care services, as well as access to newer or alternative therapies. It is thus essential that local ethics committees have the knowledge, expertise, competence and authority to review and both approve and reject - when appropriate - clinical trials.

REFERENCES

INTRODUCTION

The term ‘vulnerability’ is often used within a research ethics context, and most ethical guidelines include a section on ‘vulnerable populations’. These populations include pregnant women and foetuses, children, the mentally or physically handicapped, prisoners and other captive participants (e.g. students). (1) Pregnant women are specifically included as a category, in order to protect their unborn babies in the context of clinical trials. Broader definitions can be found in such international research ethics guidelines as the Council of International Organizations of Medical Sciences (CIOMS) Guideline 13, which describes vulnerable persons as “those who are relatively or absolutely incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests …” (2 p. 51) The limited ability to provide truly informed consent is thus often a key factor contributing to research vulnerability. CIOMS provides a fairly extensive list of groups or classes of people who may be vulnerable, including the elderly, people receiving welfare, homeless people, nomads, refugees, and patients with incurable diseases, among others.

RECs should ensure that investigators provide a clear justification for involving vulnerable persons or groups in their research, and, in particular, that the rationale is not motivated by such factors as expedience, convenience or lower cost. CIOMS requires that the following criteria be satisfied before approval for such research can be given:

- The research cannot be done involving a less vulnerable group.
- The research is directly relevant to the needs and the health concerns of this particular group.
- The research participants will have reasonable access to the benefits of the research, such as to new diagnostic or therapeutic modalities. (2)
RESEARCH VULNERABILITY AND EXPLOITATION

A vulnerable research participant is an individual, or a group of individuals, who, because of some characteristic or set of circumstances may be at risk of being exploited or harmed during the enterprise of biomedical research. This does not mean that they will be harmed, or even that they are likely to be harmed, but the fact that the person or group qualifies to be termed a ‘vulnerable research participant’ places an extra obligation on the REC to ensure that risk of harm is minimised and, in particular, that the validity of the consent process is maximised.

The issue of vulnerability has gained prominence in the context of multinational research that is initiated and funded by well-resourced countries, but which takes place in poorly resourced developing countries, but is equally important in terms of locally funded research. Research participants may have a different world view than the researchers and/or may be inadequately educated and/or have a different understanding of causality of disease or autonomy. (1)

Exploitation, in the context of research ethics, means that the benefits and burdens of the research are unfairly distributed. Emmanuel describes five characteristics of exploitation:

- The exploiting party must gain something from the exploitation.
- The ‘exploited’ party, despite gaining something from the situation, can still be exploited by it.
- Consent is insufficient to make the exploitation acceptable.
- One can be exploited without being vulnerable.
- To prevent exploitation the benefits and burdens of the endeavour (e.g. a research study) should be fairly distributed. (3)

The fair selection of research subjects is one of the ‘benchmarks of ethical clinical research’, as described by Emanuel et al. (4) In essence, this means that the research study in question, and, by implication, the research question, must be directly relevant to the population, or to the group of individuals selected as participants for any research project. The knowledge generated, must at least have the potential to contribute, even if only in the long term, to some form of benefit, or to new knowledge that is relevant to the research participant population.

CATEGORIES OF VULNERABLE RESEARCH PARTICIPANTS

Most international research ethics guidelines refer to four main groups of participants as being vulnerable, namely children, pregnant women and foetuses, persons with mental disabilities, and prisoners. (2, 5) The South African guidelines avoid using the term
'research vulnerability', referring instead more broadly to 'research requiring additional attention'. More specifically, minors, persons with intellectual or mental impairment, disabled persons, persons in dependent relationships, persons participating in research as groups, and pregnant women are all considered to be vulnerable. Furthermore, particular kinds of research projects, including projects that are undertaken in an emergency or intensive care setting, and research necessitating some form of ambiguity or deception, also deserve special attention. (5) Macklin also points out that, while women in general cannot be considered to be a vulnerable group, it is a reality that women in many developing world countries are vulnerable to exploitation, due to patriarchal family structures, or to other cultural practices. (6)

A short discussion of the four main categories follows.

**Children**

Children are always considered as a vulnerable research group, in part due to their evolving decision-making capacity, so that, in many countries, specific laws regulate their involvement as research participants. RECs must, therefore, be familiar with relevant national and international regulatory frameworks, particularly where the research is funded by an external funder, such as the National Institute of Health (NIH) in the United States (US). (See Chapter 13 for a more detailed discussion.)

**Pregnant women and foetuses**

Many types of descriptive, observational or epidemiological research studies do not pose a particular risk for pregnant women and they are therefore not vulnerable. However, interventional studies, including clinical drug trials, should only be undertaken in such a population if they are directly relevant to the health needs of the pregnant woman and her unborn child, with a direct chance of benefiting them, and no other means of conducting the research exists. Such studies should be preceded by appropriate animal studies which determine the teratogenicity and mutagenicity (see CIOMS Guideline 17). (2) The US Code of Common Federal Regulations CFR46.24 provides additional specific and important guidelines (which are mandatory requirements if the research is funded by US federal funds). (7) Any risk to the foetus must be least potentially possible, and full informed consent must be obtained from the pregnant woman, as well as, where possible, from the father of the unborn child. In addition, the individuals who are engaged in the research can have no part in determining the viability of the foetus, or in deciding that a termination of pregnancy is warranted. In other words, a clear separation must exist between care and research.

The alternative and critically important perspective on this issue, though, is that, because of the degree of protection given to pregnant women, drugs go through the full development process without being tested in pregnant women. Safety and toxicity
profiles for pregnant women therefore remain unknown. Examples include anti-malarials and antiretroviral drugs, directly relevant and required by pregnant women, which leads to off-label drug use.

Persons with intellectual or mental disability

Persons with mental disability may well not be able to provide informed consent for research, so that the required consent must be obtained from a legal guardian or caregiver. However, as with obtaining assent in research involving children, appropriate information should be provided, and assent obtained, where possible. The three general conditions that were earlier discussed in terms of research involving vulnerable persons apply equally in this context. In particular, the research question must be directly relevant to persons with mental disabilities, and it must be essential to carry out the research using this group. In other words, it must not be possible to answer the research question by involving participants without mental disability.

Prisoners

Prisoners are considered to be a vulnerable research population because their incarceration is likely to impact on their ability to make a voluntary decision as to whether or not to participate in research without coercion. When RECs review research involving prisoners, they must ensure that the majority of REC members have no affiliation with the prison system, but that at least one member should have the appropriate background to be able to represent the interests of prisoners. For example, a fitting member could, in such an instance, be an ex-prisoner. The criteria that are discussed above (namely, relevance and necessity) also apply to research involving prisoners.

AN ALTERNATIVE CONCEPTION OF RESEARCH VULNERABILITY (KIPNIS TAXONOMY)

An alternative approach to the concept of research vulnerability has been developed by Kipnis, who describes it as a “taxonomy of vulnerability”. (8) It is a useful approach for understanding some of the particular characteristics that contribute towards the potential for being exploited as a research participant, or for being included in a research project without being able to provide truly valid informed consent. Table 1 below is an adaption of a previously published version by the first author. (1, 8)
Table 1: An adaption of Kipnis’s taxonomy of research vulnerability, with examples (1, 8)

<table>
<thead>
<tr>
<th>Classification (Alternate term in brackets)</th>
<th>Questions</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Cognitive (Mental capacity)                 | Does the research participant (RP) have the ability to reflect on and decide whether or not to take part in the study? | ▪ The RP is intellectually challenged.  
  ▪ The RP is subject to such barriers to understanding as a language difference, lack of education, or a different ‘world view’ of concepts, such as not subscribing to the biological model for disease causation. |
| Juridic (Authority-vested interest)         | Is the RP subject to the authority of others who may have an independent interest in his or her participation? | ▪ A large mining company is the ‘authority’ conducting research to establish the prevalence of HIV among its workforce.                            |
| Deferential (Power imbalance)               | Is the RP used to behaving in a subordinate manner, which may make it difficult for him or her to refuse to participate in the research? | The RPs are:  
  ▪ soldiers in the military;  
  ▪ students;  
  ▪ prisoners, or  
  ▪ patients in academic hospitals. |
| Medical                                     | Has the RP been recruited because he or she has a serious health-related condition for which there are no satisfactory remedies? | The RPs are willing to take part in the research because:  
  ▪ they suffer from cancer, and the study forms part of oncology research, or  
  ▪ they are willing to participate in HIV/AIDS research to gain access to new antiretroviral treatment that is otherwise not easily accessible. |
| Allocational (Undue inducement)             | Will participation in research provide the RP with benefits to which they would otherwise not have access? | The RPs, by taking part in the research, seek to:  
  ▪ avoid having to wait in long queues at a health care facility, or  
  ▪ receive payment for taking part in the research (which, although not always problematic, could be). |
| Infrastructural                             | Does the political, organisational, economic and social context of the research setting possess the integrity and resources required to manage the study? | ▪ Due to the research being multinational in nature, it is undertaken in a country lacking the capacity for ethical review of the research.  
  ▪ Trained staff and interpreters are unavailable. |
| Social                                      | Does the RP come from a socially undervalued community?                   | The RPs are:  
  ▪ HIV-positive women living in a rural part of Southern Africa;  
  ▪ gay people living in a homophobic area in Africa;  
  ▪ refugees, or  
  ▪ commercial sex workers. |
ADDITIONAL CONSIDERATIONS
IN AN AFRICAN CONTEXT

Besides the above four types of vulnerable groups, in the African context, researchers and RECs need to be additionally cautious when dealing with research that targets the groups described below. Particularly, the RECs have to ensure that researchers have taken adequate measures to ensure that the individuals are not made worse off as a direct result of their participation in the research.

Refugees

The wars that are currently being waged in many parts of Africa mean that there are large numbers of refugees in some parts of the continent. Of the approximately 25 million refugees in the world today, 15 million are to be found in Africa. The mere fact of being a refugee means that an individual can often find herself in a subordinate position. As refugees living in refugee camps also have limited choices, issues of coercion and undue inducement require serious consideration. They are also susceptible to various mental and health problems, and may therefore become the population of focus for health research for reasons that may be both justifiable (where the research addresses health problems that are specific to the needs of refugees) and unjustifiable. An example of the latter is where the presence of a large number of individuals in a refugee camp makes it easier and more cost-effective to implement research there, even if there is no direct relevance to refugees.

Many other factors contribute to the research vulnerability of refugees, including the lack of political status and the fulfilment of basic human needs, the often low levels of literacy present, especially in long-standing camps, a poor awareness of human rights, and a tendency to obey and trust doctors (i.e. the therapeutic misconception). (See Chapter 11 for a discussion of this concept.)

RECs should consider the basic research ethical principles when reviewing protocols involving refugees as participants. Issues of providing valid informed consent, protection from coercion or undue inducement, and fair recruitment strategies are especially important where refugees are involved. (9) The protection of refugees must start with the early development of research proposals in order to maximise the benefits of involvement for the participants. Researchers should therefore make every effort to involve refugee communities throughout the entire research process. When approaching refugees as individuals or as a group to request their consent to participate in a study, the researcher must ensure that they are free to decline such a request, and that they do not feel obliged to participate in the study. (9) Protecting refugees must be a priority for the RECs that work in areas where there is a refugee presence. RECs need to consider developing special guidelines in their own SOPs for research involving refugees. Also, when reviewing research involving refugees, persons who would be considered refugee
advocates, such as members of non-governmental organisations (NGOs) working with refugees, or elected leaders within refugee communities, should be present at the REC meeting and contribute to the discussion of the research proposal. These advocates should also be included in the on-going monitoring of the research.

**AIDS orphans**
See chapter 13.

**Special groups**
Many groups of people in Africa may well be stigmatised for various reasons. Singling out a specific group for a research study has the potential of further alienating them, or of worsening the stigmatisation. For such research, it is important that additional protective measures exist to ensure that the research does not lead to the identification of the individuals by the general community. Examples of characteristics or behaviour that could lead to stigmatisation, particularly in Africa, include albinism, infertility, the practice of homosexuality and the practice of 'witchcraft' or divination. Examples of stigmatised groups, which are not specific to Africa but which are just as relevant, include groups consisting of commercial sex workers and substance abusers. Involvement in such research could even potentially lead to the identification, and to the subsequent incarceration, of such individuals. Thus, for research that particularly targets these types of individuals, there is a need to ensure that the researchers have devised ways of minimising the negative effects of the research on those concerned.

RECs must ensure that researchers fulfil their obligations: respecting all participants in the research, whatever their background, and that this is done with maximum objectivity, without prejudice, and with great care, so that they may avoid any risk of harm for those involved.

The use and dissemination of potentially sensitive information or data requires serious consideration. In general, sensitive information usually refers to any information that, if disclosed, could cause an upset either to individuals, groups or organisations. The following categories of information could be deemed as being 'sensitive.' They relate to a person's:

- racial or ethnic origin;
- political opinions;
- physical or mental health condition;
- sexual life;
- religious beliefs, and
- criminal activity or law-breaking behaviour.
For research that deals with such individuals, the REC needs to ensure that the researchers use coded forms (without names) most of the time, and that they keep the details relating to the codification in secured computer files (under the protection of passwords and not accessible via the internet) or in closed cabinets.

**Illiteracy and language barriers**

Africa, as a continent, has the highest illiteracy rate in the world. (11) Illiteracy cannot automatically be equated of vulnerability, because the process of providing informed consent should be an interactive one that does not have to rely on an ability to read. However, RECs and regulators place much emphasis on obtaining written consent and, sometimes, getting a signature or a thumbprint on a form can be seen as being more important than ensuring that the decision-making involved is informed. Also, illiteracy can contribute towards the heightened perception, from the perspective of the participant, of the existence of a negative power imbalance between themselves and the researcher (which is a form of deferential vulnerability, in terms of Kipnis’s taxonomy described above). This perception, in itself, can impact negatively on obtaining valid informed consent.

The REC must require researchers to put appropriate measures in place in order to support this special group. Consent forms, if used, must be written in very simple language, and can also be illustrated with simple line diagrams or pictures that are age appropriate. Care must be taken to avoid wording or illustrations that could be interpreted as being patronising or humiliating.

In international research consent forms are usually written in either English or French, and then translated into one or more of the local languages. In regions with multiple languages or dialects, it is unfair to expect research participants to sign a document in a language that they can neither read nor understand. Even if the participants and the researchers speak the same language, there are often major challenges to ensuring that there is effective communication between them. This adds to the common difficulties of having to provide an explanation of medical terms that are not common in many communities. Using local interpreters is often helpful, but care must be taken to avoid breaches of confidentiality, particularly when special groups, as described above, are involved.

**Poverty**

Poverty refers to the lack of fulfilment of basic human needs that is faced by many people in Africa. Despite having a wealth of natural resources, African nations are at the bottom of any list measuring economic activity, such as those stating income per capita or gross domestic product per capita. (12)
Poverty-stricken communities often lack access to adequate health services, and, thus, any medical services or other benefits that are offered by researchers in the context of a research project can act as an inducement to participate in the research. RECs need to be sure that adequate measures are in place to protect participants from exploitation and undue inducement.

**CONCLUSION AND RECOMMENDATIONS**

RECs have an added duty of care in those cases where the research involves potentially vulnerable populations. While being vulnerable does not equate to being harmed or exploited, it does increase the probability or risk that harm or exploitation could occur in a research context. The following points are especially important in this context.

1. **Community engagement.** It is essential that research involving vulnerable groups is sensitive to the needs of the research population, and that, where appropriate, the researchers should actively engage, on an on-going basis, with representatives of the group or community concerned. Furthermore, RECs may wish to include a representative of the research population as a community representative on the REC. For example, an REC that regularly evaluates research, involving children with HIV, may consider including a mother of an HIV-positive child as a community representative on the REC. (See Chapter 19 for more information regarding community engagement.)

2. **Informed consent.** The risk of obtaining informed consent from research participants whose consent is not truly informed or voluntary, or who do not truly understand the nature of the research involved, is a critical issue in this context. Hence, attempting to ensure that valid informed consent is obtained is a key REC responsibility, particularly where vulnerable populations are involved. This responsibility includes ensuring that both the informed consent form and the entire information and consent process maximises the possibility of obtaining truly valid informed consent. RECs may also need to require some form of independent assessment, or monitoring, of the process.

3. **Active monitoring.** RECs often cite the lack of both human and financial resources as being a reason for the difficulty of ensuring ongoing active (on-site) monitoring of research projects after approval. However, when very vulnerable research participants are involved, the REC should attempt to ensure that some form of active monitoring does occur, even if such monitoring is reserved for projects involving vulnerable participants. (See Chapter 8)

4. **Risk–benefit evaluation.** This component of the REC evaluation of research is always important, but it is never more so than when vulnerable research communities are involved. The REC plays a gatekeeper role, and has the ability to protect vulnerable communities and persons from research that is not in their best interests, by refusing to approve the project. However, an REC must also be careful to avoid adopting a paternalistic stance, particularly when there is the potential for benefiting at individual
or community level. Often, an approach that seeks to reduce vulnerability by other methods, as discussed in the preceding points, is preferable. (See Chapter 10)

5. The concept of vulnerability can be extended beyond research participants and communities to include vulnerable institutions and countries. In the context of international research, it is possible for institutions and countries to be exploited, with the RECs playing an additional role in ensuring that this does not happen. The chapter on research specimens addresses some of the issues dealt with in this respect. (See Chapter 17)

REFERENCES

11. http://world.bymap.org/LiteracyRates.html (Online) (Accessed 05/06/2014)
INTRODUCTION

Children have an inherent right to life and should benefit to the same extent as adults from improved health care interventions and novel medicines, as well as from social science and educational interventions. (1) They are entitled to the recognition of, and the respect for, their full human rights, as documented in the Convention on the Rights of the Child, in which a child is defined as a person who is under the age of eighteen years, unless the age of majority, by law in the territory concerned, is younger. (1) The guiding principle is always the best interest of the child, and research involving children is therefore subject to the same ethical guidelines as adult research. (1, 2)

The historical evidence of paediatric research demonstrates that children, as research participants, have, in the past, been exploited, resulting in child abuse. (3) One major example is the Willowbrook hepatitis study, in which mentally disabled children were deliberately infected with Hepatitis B to study the natural course of the disease. (3, 4) The historical evidence of harmful paediatric research has led to the necessity for additional protective measures to be built into research ethics guidelines. (5, 6) Children should be excluded from all research if there is sufficient knowledge about the subject matter, if the research results will be irrelevant to children, or if the subject matter is too scantily informed from adult or animal research. (2)

Researchers must be competent in managing childhood issues such as health, education or other social interactions and have an in-depth knowledge of the evolving physiology, psychology and cognitive ability of the child when undertaking paediatric research.
It is important that any risks are minimised, including any discomfort to the child participant. The membership of the research ethics committee (REC) must include paediatric expertise and the REC should establish that the research team has the necessary skills that are required for the research to be undertaken.

**ETHICAL ISSUES IN PAEDIATRIC BIOMEDICAL RESEARCH**

**Lack of safety and efficacious medicine data**
Children, as growing human beings, differ from adults in their physiology, development and psychology. (7, 8) Growth is particularly rapid during the first two years of life, with babies doubling their birth weight by six months of age, and tripling their weight by the age of one. The physiological changes include changes in body water compartment, muscle stores, skin surface area, and organ size, as well as function. As many such changes influence drug metabolism, the pharmacokinetic profile of drugs can, therefore, not be extrapolated from adults. Currently, nearly 50% of drugs used on children have been inadequately tested on children, which necessitates the involvement of children in clinical trials with potential benefit for them. (9)

**Painful research procedures**
Research procedures are often invasive and painful, which may cause anxiety and fear in the child participant, especially in the young child with limited cognitive capacity. (7) Researchers are therefore obliged to minimise such procedures to the maximum extent possible, always aiming at acting in the child’s best interest.

**Rare diseases and diseases limited to childhood**
Certain diseases are unique to children, which means that the research can only be done on them. (7) Examples of such diseases include the clinical trials undertaken for the administration of exogenous surfactant to premature infants, with the intention of preventing respiratory distress syndrome (RDS). (10) Only premature infants develop RDS, due to a lack of endogenous surfactant in their lungs. Such research could therefore not be conducted on adults, demonstrating the need for these kinds of clinical trials to be conducted on children to ensure that they benefit from advances in modern medicine.

**Placebo-controlled trials**
Placebo-controlled clinical trials on children are only allowed under very stringent inclusion and exclusion criteria. Inclusion criteria include the following:

- an asymptomatic or mild primary condition;
- the absence of target organ damage or risk of deterioration;
Children as research subjects

- short duration of the trial (4–8 weeks being an acceptable time frame), and
- close monitoring to mark any deterioration, or immediate exit if a worsening of the condition is observed.

The exclusion criteria are:
- where there is a definite risk of the condition under investigation worsening, and
- if the patient is already seriously compromised due to the disease.

The choice of a control group in placebo-controlled trials is problematic, since active therapy will not be provided for the control group. For children in the control group, only minimal risk should be involved. A compelling scientific argument should also exist for the need to determine the safety and efficacy of the drug or intervention under investigation.

ETHICAL ISSUES IN PAEDIATRIC PSYCHOSOCIAL AND EDUCATIONAL RESEARCH

Misunderstanding and limited attention span

In addition to the researchers who undertake paediatric social science research having the necessary competencies to undertake such research, they should also have an in-depth knowledge of the psychology of the child. (11) As children's cognitive ability and vocabulary are still developing, there is a great risk of misunderstanding the younger child's response, or even of the child misunderstanding the questions or procedures being presented to them. Children also tend to have a limited attention span, and tend to be more prone to fatigue in the research setting than are adults, which may influence the research outcome, with potentially greater risk of the early termination of participation.

Deception and simulations

Risk assessment should take the developmental stage of the child participant into consideration, as such stages may vary from the complete lack of an ability to understand issues to the presence of a decision-making ability, as in adolescence. (11) The use of deception or simulation is problematic in social science research. Practising deception towards a child may so seriously compromise his or her trust in adults that it becomes harmful. Good motivation for the use of deception with children is therefore required. The use of simulations may also cause a child distress, with such distress lasting even after the completion of the research.

RISK CATEGORIES IN RESEARCH

Risk assessment is a crucial task for both the researcher(s) and the REC to undertake, in order to ensure that children are adequately protected during the research process (see chapter 10 for a more detailed discussion). (2, 5, 6) The assessment of risk should be
done in a way that gives all due consideration to the perspective of the child. Allowable risk for research with direct benefit is permitted if the risk occurs under conditions of research equipoise. If there is no direct benefit to be gained from the research, only minimal risk or ‘minor increase over minimal risk’ is allowable. (2, 6) Minimal risk is defined as risks that are associated with everyday risks in the life of a normal, healthy child. (2) Reasonable differences of opinion exist regarding what constitutes minimal risk in the daily life of healthy children in a stable society.

Since the assessment of minimal risk is essential in the review of paediatric research with no direct benefit, it is important to assess each procedure or intervention separately (see component analysis in the chapter 10). (2) No procedure or intervention that is only aimed at answering the research question should be allowed if there is more than minimal risk involved.

Risk for paediatric research can be categorised into one of the following four categories:

- research that poses no more than minimal risk, where risk is defined as the potential risk of everyday life in a healthy child living in a stable society; (2, 6)
- research that poses more than minimal risk, but with potential direct benefit to the individual child; (2, 6)
- only minor increase over minimal risk, with no potential for direct benefit, but which is likely to lead to the development of generalisable knowledge being generated for the class of subjects concerned, (2, 6) and
- other research that does not address the above-mentioned risk categories. (2, 6)

In the case of the first three of the categories above, the requirement for participation is parental informed consent, as well as the child’s assent, where the child is seven years old or older, although on occasion younger children may also be able to give assent if cognitively mature for their age. (6) In the case of the final category – other research – in addition to requiring the consent of both the parents and the child, the approval of the ethics review committee – including particular paediatric expertise – is needed.

Many guidelines contain problematic definitions regarding the different aspects of participation in paediatric research, with research often classified as being of a therapeutic nature if it involves the application of a treatment, or being regarded as non-therapeutic if it is undertaken for other purposes, and can only be allowed if the potential benefits outweigh the risks. (12) These definitions are currently included in the South African National Health Act, 2003 (Act no. 61 of 2003) (Section 71:3) and pose major problems for non-therapeutic research involving children, since ministerial consent will be required regardless of which risk category is involved. (13, 14) Therapeutic research should adhere to the International Conference on Harmonisation’s guideline for good clinical practice, and researchers should also strive their utmost to ensure that they minimise the amount of pain and risk for participants.
CHILDREN’S PARTICIPATION IN DECISION-MAKING

Parents are, traditionally, the primary decision-makers for their minor children and they therefore frequently exercise the right to make proxy decisions for their children regarding participation in research. (2, 15) Children are particularly vulnerable in terms of research due to their lack of capacity to give their consent, and therefore their protection, in such terms, tends to rely on the third-party consent of the parent or legal guardian. In South Africa parental consent is mandatory. (13, 16) Parents and health researchers may have interests that conflict with the best interest of the child. Parents, for example, may consent to their child participating in a phase 1 cancer trial due to their hope that such research will result in a cure for their child’s cancer, or they may have other interests that are undisclosed. The REC should therefore establish, in an objective manner, what the best way forward is for a child in a given research scenario. The parental consent process also takes time, hence the associated emotional and rational conditions must be taken into account. Parents must not give consent if they feel that it is against their child’s interest. It must be noted that consent from the parents or guardians of the child does not absolve the researcher from liability if the child is injured during the research process. The researchers should, consequently, provide details of the informed consent process, which involves both parents and child participants, to the REC for review.

The assent of the child should be sought if he or she has the ability to understand the content of the research question and its expected outcome. In the given context, assent is a process whereby the child indicates his or her agreement to participate in a particular research process. (2) As enshrined in the Declaration of Helsinki, children’s assent is linked to the degree of understanding and level of maturity. (5) The generally acceptable age for assent is seven years of age, since, by then, a child has developed the necessary cognitive ability to understand the essential facts relating to the proposed research, and can deliberate what its immediate outcome will be. The information provided to the child should be understandable to them, taking into consideration their level of understanding and cognitive development. If the child refuses to participate in the research, no incentive should be offered that will coerce the child into assenting to it. Keep in mind that a child may be deferential to their parents and/or the researchers and their deference may mask their unwillingness to participate in the research. Such an attitude holds especially true for the younger child, who is more likely than the older child to do what they perceive their parents or other adults want them to do. The situation may be exacerbated if the child is from a cultural background that expects such behaviour as the societal norm. (17) It is therefore necessary that researchers build in a process to obtain child assent in such a way that the child’s true understanding and willingness to participate in the research can be determined. Usually the REC is deemed able to determine whether child assent is necessary or whether waiver of assent can be given. (2)
Adolescents are a particular group of minors that may pose challenges regarding consent. The REC may be willing to consider waiving consent if the age of majority is recognised as being reached at a younger age in a particular country or in the context of child-minded families, where the child, who heads the family, is deemed competent, and where the child can consent to receiving medical treatment, similar to the research, without parental consent. (18) The REC, in such cases, would have to determine whether the child has the capacity to provide informed consent.

VULNERABLE CHILDREN

Although all children are, in a sense, vulnerable due to their reliance on adults for protection, certain classes of children may be even more vulnerable within the research domain. (19) These classes of children include dying children; children who, due to being institutionalised (orphans), lack a caregiver with a direct emotional link to the individual child; or children from severely poverty-stricken communities. These children require additional protection, including that of paediatric expertise on the ethics review committee. This class of vulnerable groups may also require additional protection in the form of an ombudsman or physician who is not part of the research team to monitor the research process in the best interest of the individual child.

Dying children

Dying children as research participants are particularly vulnerable, since both the child and the parents are under tremendous emotional stress due to the underlying disease, which may impact negatively on the consent process. Research in such a context can therefore pose even greater invasion of privacy and exploitation than usual.

AIDS orphans

Millions of children across Africa are considered to be AIDS orphans. Such an orphan is a child whose mother has died, due to AIDS, before the child’s 15th birthday, regardless of whether the father is still alive. (10) Much stigma is still associated with HIV/AIDS in many parts of Africa, with AIDS orphans possibly being looked down upon by communities. Children, who especially lack the advantage of the protection of a guardian or primary caregiver, constitute a particularly vulnerable group. When reviewing research involving AIDS orphans, similarly to refugee research, the REC should co-opt a suitable advocate to participate in the review process (see chapter 14).

AIDS orphans usually cannot give their legal informed consent to participate in a study because they are minors. Issues relating to the legality of consent processes tend to vary, depending on the laws and regulation of the country where the research is being conducted. It is thus essential that an REC be familiar with its own national regulatory framework, as well as with those of others that may apply (for example, if the research is funded by the US federal government).
USEFUL CHECKLIST IN THE ETHICS REVIEW OF PAEDIATRIC RESEARCH

- The research is justified in relation to children (19, 20) if:
  - the condition involves children for whom there is potential direct benefit;
  - some potential benefit may become available for the specific class of participants in future;
  - the necessary data cannot be obtained or extrapolated from adult data, or
  - the necessary pre-clinical (e.g. animal studies) have been conducted if applicable.

- Risk should be minimised to whatever extent is possible.

- The research team has the necessary paediatric expertise and understands the needs of children.

- The physical research environment is safe and conducive to the activities of children.

- The research team has taken adequate measures to minimise the amount of pain and discomfort to participants. This includes the minimising of painful procedures, as well as taking into account prior exposure to medical interventions for the disease that may already have caused distress to the child participant.

- The intended number of children to be recruited is the absolute minimum – allowing for the collection of the necessary data that will lead to statistical significance – required to answer the scientific question.

- The procedures and invasive technology used should be the least invasive available, both from a physical and a psychological perspective.

- Adequate discussion of all information should be undertaken with the parents or legal guardian, with full disclosure of all the potential risks.

- The child should participate in the decision-making process of informed consent through the provision of assent if he or she is able to understand and participate in the process. Such participation is usually permissible from the age of seven years onwards. The withdrawal of assent should also be allowed and discussed in terms of the research protocol.

- The privacy of the child should be protected and should be discussed in terms of the research protocol as regards what measures the researchers will undertake to ensure that such privacy is respected.

- The parents or a legal guardian who is capable of providing emotional support should be present at all times.

- Certain classes of children are even more vulnerable, including dying, orphans, the homeless child, the institutionalised child, and those with learning disabilities. Research should only involve such children if there is true potential benefit for the individual child.

- Ethics review committees should ensure that children with rare diseases do not become professional research participants.

- Payment for research participation should only involve out-of-pocket expenses, due to the risk of undue coercion. However, the child participant may benefit from a small gift for their participation.
REFERENCES

WHAT IS PUBLIC HEALTH? (1)

There are many different definitions of ‘public health’, ranging from fairly broad to much narrower ones. One of the most often quoted and most detailed definitions comes from an article published in 1920 by CEA Winslow. (2) This definition is particularly useful because it lays down an initial platform for any discussion as to what is, and what is not, public health:

> Public health is the science and art of (1) preventing disease, (2) prolonging life and (3) organized community efforts for (a) the sanitation of the environment, (b) the control of communicable infections, (c) the education of the individual in personal hygiene, (d) the organization of medical services for the early diagnosis and prevention of disease, and (e) the development of a social machinery to ensure everyone a standard of living adequate for the maintenance of health, so organizing these benefits as to enable every citizen to realize his birthright and longevity. (2 p.183)

A broader definition of public health is given by the Institute of Medicine (IOM) in its 1988 report entitled *The Future of Public Health*. The IOM definition has three parts, namely (1) mission; (2) substance; and (3) organisational structure:

1. The mission of public health is the fulfilment of society’s interest in assuring the conditions in which people can be healthy.

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1 Gabriel Mwaluko passed away suddenly in November 2013. His contribution to this chapter and volume is acknowledged and greatly appreciated. Certain sections of this chapter, particularly this section, come directly from the PhD thesis of the first author.
2. The substance of public health consists of organised community efforts that are aimed at the prevention of disease and at the promotion of health. It links many disciplines, and rests upon the scientific core of epidemiology.

3. The organisational framework of public health is the structure that encompasses both activities undertaken within the formal structure of government, and the associated efforts of private and voluntary organisations and individuals. (3)

The Royal College of Physicians in the United Kingdom defines public health as: ‘The science and art of preventing disease, prolonging life and promoting health through organized efforts of society.’ (4) The Nuffield Council on Bioethics also uses this definition, but adds two notions that are of particular significance, namely the importance of prevention, and the notion that public health is achieved by means of ‘collective effort.’ (5)

The World Health Organization (WHO) is regarded as the ‘public health arm’ of the United Nations and promotes a broad conception of health as an ideal state of mental and physical well-being, which underpins its approach to public health. (6)

In summary, a useful notion of public health that is particularly suited to a developing world context is that ‘public health is about the health of “societies” and “communities” rather than the health of individuals, and it involves all those spheres of health, where collective action by governments and other organizations can make a positive impact.’ (1) p.32.

**PUBLIC HEALTH ETHICS**

The development and implementation of public health policies, programmes and research studies may raise many ethical issues and challenges. These ethical issues are often framed as a tension or contest between individual autonomy, rights and interests and the interests of the community or broader public, sometimes also described as the ‘common good’. Public health ethics also often involve issues that are related to social justice and global justice. The field of public health ethics has developed significantly over the last decade and an in-depth discussion of the subject is beyond the scope of this chapter, which is primarily focused on public health research ethics, rather than on public health ethics per se.

A brief discussion of three separate dominant frameworks for public health ethics will be followed by an introduction to Mill’s harm principle, as a basic understanding of these frameworks is important for REC members reviewing public health research protocols. The first of these frameworks is the ‘human rights approach,’ which was shaped predominantly by the HIV/AIDS epidemic during the 1980s and 1990s. The second is a modified version of ‘principlism,’ while the third approaches public health ethics from a ‘utilitarian’ perspective. However, it is important to note that this is a
rapidly evolving field, and that there are alternative, more communitarian approaches to the ethical challenges of public health, such as the ‘stewardship model’ proposed by the Nuffield Council on Bioethics. (5)

**A human rights perspective**

The human rights approach to public health, which has been equated to a ‘societal analysis’ of health, requires ‘uncovering the rights violations, failures of rights realization and burdens on dignity which constitute the societal roots of health problems’. (7, 8) Issues that are related to public health often adversely affect the most vulnerable members of any community, thus taking human rights into consideration, when making public health policy decisions, is very important. However, within the context of public health, individual rights often come into conflict with the needs and interests of the public or community as a whole, thus limiting the usefulness of this approach in some contexts.

**A principle-based approach**

The most influential text within the field of bioethics is, arguably, the *Principles of biomedical ethics*. (9) The principle-based approach, which describes the four principles of bioethics (namely beneficence, non-maleficence, autonomy, and justice underpinned by a theory of ‘common morality’), has shaped the field of bioethics over the last three decades. It is, therefore, not unexpected that when scholars in the field of bioethics started to discuss the need to articulate the reason for an ethical framework for public health, a similar approach may well have been thought to be appropriate. This approach to public health is discussed in more detail by Childress *et al.* (10)

**A utilitarian approach**

Utilitarianism as a moral theory was first articulated by David Hume (1711–1776), but it was later fully developed by Jeremy Bentham (1780–1832) and John Stuart Mill (1806–1873). This moral theory is based on one principle only the principle of utility. The principle of utility dictates that the morally right act is the one that maximises value over ‘disvalue’. (11 p. 4) In other words, what makes an action right, are its consequences. Within the context of public health, this principle can essentially be interpreted to mean that the right policy or practice is that which produces the most benefit for the greatest number. The theory is entirely outcomes focused, and it is easy to see that it seems to be ideally suited to the domain of public health, because the aim is to maximise health benefit for as many as possible, which is what public health is generally all about – improving health outcomes at a community or population level rather than at an individual level.

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2 This address was republished almost a decade later in the American Journal of Public Health.
3 ‘Disvalue’ is a term used by Bentham and Mill to mean anything that would be considered the opposite of anything ‘of value’.
A second important component of utilitarianism, from a public health perspective, is impartiality, or, as Bentham supposedly stated: ‘Everybody to count for one, nobody for more than one.’ (12 p. 82) When the balance of value and disvalue are being calculated, all parties affected must be considered from a disinterested, impartial point of view. Public health is concerned with health at a population level, and not at an individual level. Thus, a theory that is impartial and regards everyone’s interests as being equal, no matter where one stands in the social order of things, would be particularly suitable within this context.

**Mill’s harm principle**

An aspect of Mill’s philosophy, which is perhaps not central to the theory of utilitarianism, but is particularly relevant to the field of public health, is what is known as Mill’s harm principle. Mill states that “the moral rules which forbid mankind to hurt one another (in which we must never forget to include wrongful interference with each other’s freedoms) are more vital to human well-being than any other maxims”. (13 p. 13) According to this principle, the only justifiable reason to interfere in someone’s personal autonomy or freedom is to prevent them from harming others; beneficence alone is not a good enough reason to override individual autonomy.

**PUBLIC HEALTH RESEARCH**

**The nature of public health research and how it differs from clinical research**

The discussion above emphasised that public health is primarily about the health of societies or communities, rather than about individuals. Thus public health research is aimed at assessing whether or not a particular intervention is effective at a community rather than at an individual level. The primary object of interest is the community, rather than the individual. Outcome measures are focused at a community level.

Table 1 below compares hypothetical examples of public health research and clinical research for tuberculosis (TB), malaria and HIV.

**Table 1: A comparison of public health research and of clinical research for tuberculosis, malaria and HIV**

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<th>Public Health Research</th>
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<tr>
<td><strong>Tuberculosis</strong></td>
<td>A RCT to determine the safety and efficacy of indefinite isonicotinylhydrazine (INH) prevention therapy in HIV-positive and negative mineworkers with no evidence of active TB.</td>
<td>A community-based trial to determine whether providing INH to entire communities of mineworkers can reduce the incidence and prevalence of TB at community level (14).</td>
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<td><strong>Malaria</strong></td>
<td>A study to determine whether the use of insecticide-treated mosquito bed-nets by at least 70% of the community reduces the incidence of the malaria infection in that community, compared with the incidence of infection in communities that only have access to untreated bed-nets.</td>
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<td>A RCT of artemisin-halofantrine combination therapy versus halofantrine therapy alone for the treatment of severe malaria to determine effectiveness.</td>
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<td><strong>HIV</strong></td>
<td>A community-based study to evaluate whether door-to-door health education programmes that emphasise rapid HIV testing reduce HIV incidence at population or community level more effectively than similar clinic-based programmes. (15)</td>
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<td>A study to evaluate whether the availability of free condoms, coupled with repeated intensive motivational interviewing, can reduce the incidence of recurrent sexually transmitted infections (STIs) in sex workers attending an inner-city STI clinic.</td>
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<td><strong>Diabetes</strong></td>
<td>A community-based cluster randomised study that evaluates the impact of an introduction of a ‘sugar tax’ on all products containing refined sugar on the incidence of diabetes and obesity at community level over a ten-year period.</td>
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<td>A RCT to evaluate the impact that home-based glucose monitoring has on individual morbidity and mortality.</td>
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**COMMUNITY CLUSTER RANDOMISED TRIALS (CCRTS)**

A cluster randomised trial involves clusters of individuals who are linked together by some common factor, being randomised to receive an intervention. The design is therefore similar to a clinical drug trial, but with several notable differences. The intervention being tested is usually some form of public health intervention rather than a ‘drug’, and the outcome measures are evaluated at a population or community level rather than at an individual one. Often entire communities are randomised to receive one or other intervention. Thus individuals in a community may be taking part in a CCRT without even realising it, especially if they are in the control arm (i.e. subject to no new intervention). Hence, one of the biggest ethical challenges with CCRTs is to define and to decide who is and who is not a research participant. The very nature of a CCRT means that, sometimes, literally tens of thousands of people may be directly or indirectly involved or affected by the public health intervention under investigation. Identifying all of these individuals as ‘research participants’ to whom the conventional ethical norms and standards of clinical research trials are applied, may well mean that the CCRT is no longer either logistically or financially feasible. Thus RECs have to balance the aims and objectives of the study carefully (and the importance thereof, in a public health context) with the need to protect the rights and interests of individuals and community members.

The notion of ‘informed consent’ within the context of a CCRT is particularly challenging, as some form of ‘consent’ should be sought at several levels:

- **Gatekeeper or guardian consent:** Gatekeeper or guardian refers to the entity that ‘delivers the community’, namely that gives permission for researchers to undertake
the research in the selected community. (16) Often the ‘gatekeeper’ is the government and/or the local health authority.

- **Community consent or engagement**: The notion of ‘community consent’ is a misleading one, which is best avoided. As Weijer and Emmanuel, as well as Weijer *et al.* point out, true community consent can only be obtained from communities that are governed or led by a recognised political or tribal authority, which is usually not the case. If used inappropriately, the concept of ‘community consent’ may result in a false sense of security or mandate. (17, 18) Rather, researchers should discuss in detail, in their REC applications, the proposed community engagement process, identifying both successes and challenges.

- **Elder consent**: In certain research contexts, for example rural villages, consent may need to be obtained from the recognised village or tribal ‘elder’. Once this consent has been obtained, care must still be taken to obtain individual consent and to ensure the voluntariness of individual participation.

- **Household consent**: Many CCRTs involve accessing households. This presents several ethical challenges as it may be unclear as to what defines ‘a household’, as well as whom is entitled to consent to household access. (Is ‘the household’ those living under one roof, or on one property, or eating out of one pot, or family members? Does the concept of ‘the household’ also include any lodgers?)

- **Individual consent**: Even after all the above consents have been obtained, as appropriate, obtaining individual consent from those identified as ‘research participants’ is still mandatory. Often, one of the biggest ethical challenges in a CCRT is how best to define clearly who qualifies as a ‘research participant’.

The above serves as a brief introduction to the ethical challenges presented by CCRTs. RECs are advised to refer to the Ottawa ethical guidelines for CCRTs, released in 2012, for more detailed guidance. (19)

**ETHICAL CHALLENGES IN PUBLIC HEALTH RESEARCH**

Public health research presents various unique ethical challenges, primarily because such research is focused on interventions that are aimed at benefiting communities or populations rather than individuals. Here is an introduction to some of the ethical challenges that are sometimes encountered in public health research:

- **Rights and interests of individuals versus the ‘common good’**: RECs are mandated to protect the rights and interests of individual research participants. Thus, they may experience difficulties in evaluating research projects that are unlikely to benefit individuals and that may well inconvenience, disadvantage or present some degree of risk to certain individuals, but which, nevertheless, present the prospect of benefiting communities or future populations.
Challenging and often complicated study design: Public health research studies often have very complex methodology and design, and may well combine novel public health interventions with research. Assessing both the science and the ethics of a study is therefore often particularly challenging, and RECs may need to co-opt additional public health and statistical expertise to ensure that the study is both scientifically valid and ethically acceptable.

Community engagement and community consent: Ensuring adequate community and stakeholder engagement is particularly important. RECs should expect researchers to submit a detailed community engagement plan, including a long-term engagement strategy with some form of monitoring, to the REC for review and approval.

Large numbers of participants: The testing of a public health intervention within a research context may involve entire communities, thus including many more people than are usually involved in clinical research studies. Also, as was earlier discussed, it may sometimes not be that clear as to who ought to be considered ‘research participants’ in such studies.

Informed consent: This may well have implications in respect of strategies for requiring or providing informed consent. RECs may often be asked to approve an alternative informed consent process, such as that of verbal rather than written consent, on the grounds that the study is relatively low risk, and that it would logistically be difficult to undertake if conventional methods and standards for obtaining informed consent were required. Under certain circumstances, the researchers may even request a waiver of informed consent, such as when collecting ‘routine’ health care data from a clinic. The REC must weigh the overall risks to participants, and the possible infringements of the principle of autonomy, with the potential for obtaining public benefit from a study before reaching a decision on the justification of such requests.

Vulnerable research populations: Innovative public health programmes are often most needed in communities that are considered to be particularly vulnerable. The issue is discussed in more detail in chapter 12.

Involvement of children: Many public health interventions, for example vaccination programmes, are aimed at children rather than adults. Children are generally regarded as constituting vulnerable research populations (see chapter 13). Particular ethical standards apply to research involving children, including the requirement of the prospect of direct benefit or, if there is no prospect of direct benefit, the prospect of gaining a new understanding of the child's disease or condition that could benefit similar and future children. However, public health research is often involved in promoting health and in preventing disease rather than in treatment itself. Thus the above ethical norms are difficult to apply, particularly in the case of vaccine studies that involve healthy children.

Blurred boundaries between research and public health programme intervention: The boundaries between public health research and public health implementation are often blurred, especially as new public health interventions require monitoring to
assess their effectiveness. Such monitoring might result in the systematic collection and analysis of health care data, including private health care information, without individual informed consent or REC oversight, because such information is collected as part of ‘monitoring and evaluation’ (M&E), rather than as part of research. RECs are often faced with the situation where data collection and analysis are already complete, and have occurred without ethics approval. At this point, those who are involved in the research might approach the REC to request ‘retrospective’ approval to publish the data, on the grounds that the publication is in the interest of the ‘common good’. Such grounds could apply when the public health intervention has been successful, and when the publication of the results of the programme would mean that similar programmes could be implemented elsewhere. The REC must carefully assess the merits of the application before deciding whether or not a request is justified. The consequences of denying the request, and therefore possibly of preventing the publication and dissemination of valuable knowledge, must also be assessed.

CONCLUSION

Public health research differs from clinical research because the primary focus of the research is on evaluating outcomes at a population or community level rather than at an individual level. Thus, the research question usually pertains to whether ‘X’ is best for the community as a whole, rather than whether ‘X’ is best for the individual concerned. This difference presents RECs with a new, and sometimes very complex, set of ethical challenges, particularly when it comes to evaluating the overall risk and benefit of the proposed research, and to deciding whether or not it is ethically admissible. Furthermore, the ‘traditional’ principles of research ethics are aimed at protecting the rights and interests of individuals rather than those of communities. However, individuals constitute communities and thus community health concerns are also often individual health concerns. RECs must carefully assess the risks and benefits of the proposed research for both the individuals and the community as a whole, and, by means of a process of careful balancing and weighing, arrive at a suitable overall conclusion.

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INTRODUCTION

The use of medicinal herbs is common in low-income economies, where over 80% of people use traditional medicine (TM) for therapeutic, spiritual or prophylactic purposes. Traditional health practitioners are the primary health care providers for the inhabitants of many Asian and African countries, and, in some remote regions, they even represent the sole provider of health services. (1) TM is currently characterised by a wide variety of diverging practices, which often occur in a context that lacks a solid legal and biomedical framework that may otherwise prevent potentially dangerous consequences for patients. (2) Traditional herbal medicines are “naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices”. (3) However, traditional health practices have the potential to harm when they are applied in an inappropriate or uncontrolled manner. (4)
Considering the extremely large number of practitioners who are active around the world, and the even larger population that utilises their knowledge, traditional health care raises fundamental ethical questions and requires specific reflection to deal with its ethical implications. It entails a different approach to life, death, health and illness, and a different view of the doctor–patient relationship, of health services and of risk factors for disease. (5) Traditional health practices present the challenge of finding a way in which to integrate cultural diversity and respect for individual cultures with medical obligations and the universally accepted ethical principles of respect for persons, with an obligation to ‘first do no harm’, and then to do good and to act justly.

THE NEED TO PROVE THE SAFETY AND EFFICACY OF TRADITIONAL MEDICINES

International research demonstrates an increasing awareness of the important role that herbal medicine plays in the health of many communities in Africa and elsewhere in the developing world. According to the World Health Organization (WHO), many, if not most people living in rural regions rely on medicinal plants to treat common ailments. (6) In addition, about 60% of synthetic drugs used in allopathic medicine actually have their origins in medicinal plants, emphasising the importance of plants and of traditional knowledge systems in the context of health research. Cost is also often a major factor that influences the preference for herbal medicines over synthetically produced drugs. Synthetic (‘western’) drugs are almost always rigorously researched as part of the development process, which greatly increases the production costs involved, whereas TMs are often cheaply produced using locally available ingredients. Thus, the latter are often not evidence-based, and may be unethically promoted. (7, 8) However, the efficacy of certain TMs such as Artemisia annua for treating malaria and of Taxus brevifolia (a yew derivative that prevents the division of cancer cells, and which has been successfully used in oncology treatments) is undisputed. (9)

Often, a general and unfounded assumption exists that herbal drugs are safe and generally without side effects, which is, unfortunately, not always true. Furthermore, herbal–synthetic drug interactions may pose a major safety challenge, as many people seeking health care use both western and traditional systems simultaneously. Many anecdotal reports exist of the occurrence of both hepatotoxicity and nephrotoxicity in relation to the use of various medicinal herbs. Unanticipated post-operative bleeding can often also be traced back to the concomitant use of herbal remedies. (10)

TRADITIONAL MEDICINE PRACTICE AND POLICY IN AFRICA

TM is especially used to treat infectious diseases and chronic conditions. Some governments in Africa are developing strategic plans to regulate the practice of TM,
incorporating WHO standards and guidelines. Such plans aim at bringing all the stakeholders involved in the TM practice, such as medical practitioners, researchers and traditional herbalists, together to work in synergy. (11) In Cameroon, as in many other sub-Saharan African countries, several plants have been reported to have medicinal properties that are effective against such infectious diseases as HIV/AIDS (for example, the immune stimulation action of *Ancistracladus korupensis*), hepatitis viruses, malaria, (*Enanthia chloratha*), and some chronic diseases, such as diabetes, obesity and arterial hypertension. (12) Scientists who work in the field of TM research do not always follow conventional pathways for the development and testing of therapeutic agents. Local investigators sometimes avoid preclinical stages and early clinical phases, perhaps primarily due to cost concerns, but also due to the existence of anecdotal evidence and common usage, which suggest that certain TMs are safe.

Counterfeit, poor quality and contaminated herbal products also represent a substantial and serious threat to patient safety at both a local and, sometimes, an international level. Even though natural plants are considered to be beneficial by local communities and are widely used in many circumstances, the scientific and regulatory framework for TM research needs further development in Africa. Statements like ‘*this product is of herbal and natural origin and thus carries no risk for harm*’ are potentially misleading, and should be avoided. In the development process, TM requires scientific validation of safety and efficacy, using similar steps to those that are required in a synthetic drug development process. (9)

**ETHICAL REVIEW OF TRADITIONAL MEDICINE RESEARCH**

African research ethics committees (RECs) that review research protocols involving herbal products should follow their applicable standard operating procedures (SOPs), and such protocols should be subjected to the same review processes and standards as any other scientific clinical research involving human participants. For example, an application for research involving herbal products should ordinarily include:

- a signed explanatory cover letter from the applicant;
- the study protocol and supporting documents, and
- CVs of all investigators involved with the study.

RECs should review and approve a research protocol for each study involving herbal products prior to its implementation. National and international ethical guidelines should guide the review of research protocols involving herbal products and human subjects.

RECs should assess whether the following elements are in place:

- The research team should have a team member with clinical medicine and toxicology competence.
Community indigenous knowledge and intellectual property rights should be preserved.

International standards on access and benefits sharing (ABS) should be respected.

There should be evidence that the herbal product has been subjected to rigorous toxicological testing.

Scientific evidence should be seen to support the safety profile of the herbal product (anecdotal observations should generally be regarded as insufficient supporting evidence).

Plans for benefit sharing by the community or by the participants, particularly if there is a possibility of developing a patentable product or a product that could be commercially viable, should be tangibly present.

A data safety and monitoring plan should be in position.

The process for obtaining and documenting informed consent should be clear.

Provision for confidentiality should be made.

Records of preclinical (animal) data and first-phase clinical data (if applicable) should be maintained.

ETHICAL FRAMEWORK FOR TRADITIONAL MEDICINE RESEARCH

The components of an ethical framework as outlined by Emanuel et al., include eight ethical requirements for clinical research. (3) The framework has been effectively used to demonstrate the ethical issues related to TM research by Tilburt et al., who focus, in particular, on three of the eight benchmarks, namely on social value, scientific validity, and risk–benefit assessment. (14)

Social value

All biomedical research involving particular communities of human participants must hold out some potential value for those participants. The value of research involving TMs is likely to be assessed quite differently by various stakeholders. Local health care authorities are often keen to validate the safety and effectiveness of well-known herbal medicines that are already in common use for such conditions as malaria. In contrast, clinicians are often keen to confirm their suspicions that certain TMs are toxic, and that they have the potential to harm, whereas entrepreneurs and pharmaceutical companies may well be primarily interested in reaping profits from cheaply produced medicines. (14)

Scientific validity

The scientific design of TM research studies can present significant challenges to researchers, as they must maximise the potential for achieving the stated study objectives, while simultaneously ensuring that the participants concerned are not denied necessary health care. Placebo-controlled trials in this context are, thus, particularly
challenging, although their use is justified in some circumstances. (8) (See Chapter 12 for a discussion of the ethical challenges in some involved in placebo controlled trials.)

TM research should be ‘methodologically rigorous and therefore must yield valid, reliable, generalisable, and interpretable data, must be feasible, must also be done by qualified people.’ (13) According to Tilburt et al., research on herbal medicines should ideally utilise the methodology of the randomised controlled trial (RCT), as this is currently acknowledged to be the best method for generating evidence-based knowledge. (14) However, these authors identify two significant challenges faced by such an approach. First, TMs are often individualised for each patient, and used, or administered, in many different forms and dosages, often in combination with other herbal products. Thus, determining a dose and formulation for a particular study may, in addition to being challenging, also mean that both a positive or negative outcome may not accurately reflect the actual conditions and outcome of usage in a real-life context. Second, the diagnostic criteria that are used in a TM context may not easily translate or transfer into a biomedical context, thus making the evaluation of efficacy challenging. (14) An example of the above is provided by Kaptchuk, who notes that, if American cardiologists wanted to use a Chinese herbal medicine in the context of cardiac failure, they would most likely use the New York Heart Association criteria for the staging of heart failure to measure efficacy. However, Chinese traditional practitioners would view such a situation within the context of a deficiency or excess of ‘heart yang chi’, which is a notion that would make little sense to American physicians. (15)

Favourable risk–benefit ratio

The assessment of risk and benefit of a research project is the core duty of the REC, and is particularly challenging in terms of TM research. Herbal medicines have often come into use by means of a process of ‘trial and error’ over many years. These herbal medicines are often used in various combinations, originating from various plant sources with their own various species, growing environments and active ingredients. (14) There is therefore no assessment of dosage requirements as is usually established in phase II trials. In addition, many questions have still to be answered about the actual product concerning its purity, quality, chemical stability and percentage of active ingredient. (8)

Tilburt et al. note that attempts to implement large-scale clinical research trials in the context of TM research would require reviewers on RECs to conduct a risk–benefit assessment, which is likely to be quite difficult. (14) The possible variability in active ingredient in the investigational product requires careful assessment, and should be guaranteed by study investigators and sponsors. Also, local REC members may well be familiar with the TM product, as they may even have used it themselves. Such usage may influence REC members’ objectivity when it comes to reviewing and assessing risk involving an herbal product that is familiar, in common use and widely assumed to be
safe and non-toxic. Alternatively, REC members may be completely unfamiliar with, and possibly somewhat sceptical about, the use of TM in general. They must, therefore, be sure to rely solely on the scientific evidence and the information provided in the research proposal, and avoid allowing personal prejudices and opinions to influence objective review. (14 p. 6)

Collaborative partnership in traditional medicine research

Collaborative partnerships with all stakeholders, including traditional healers, local drug regulatory authorities, local custodians of indigenous knowledge systems, and biotechnology or pharmaceutical companies are essential for ensuring the credibility of TM research and the translation of the knowledge that is gained into useful, cheap and evidence-based health products. RECs must encourage researchers, and ensure that they establish such partnerships.

CONCLUSION

In Africa and other developing countries, many, if not most, health care seekers consult traditional systems of medicine from time to time. The integration of traditional and western medicine systems could possibly assist with extending affordable, effective and safe health care to a wider section of the population than currently has access to it. There is, therefore, a pressing need for the harmonisation of the practice of African herbal TM with western medicine, through strategic policy road maps that are put in place by stakeholders and governments. TM could be used in primary health care practice if TM products were standardised and evidence-based. The creation of awareness and the concretisation of research in the sphere of TM, in conjunction with an emphasis on the importance of ethically guided research, is an increasing priority in many African countries. RECs should not hesitate to review TM research and to apply internationally recognised research ethics standards to the research.

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16

**ETHICS REVIEW OF SOCIAL AND BEHAVIOURAL RESEARCH IN AN AFRICAN CONTEXT**

Farirai Mutenherwa, Douglas Richard Wassenaar

**Key Message:** Ethics review of social and behavioural research has attracted controversy since the introduction of the research ethics committee system. In this chapter we present arguments for and against ethics review of social and behavioural studies with a view to demonstrating the value and utility of ethics review for such studies. The unique ethical challenges associated with social science methodologies are also highlighted within the African context. We recommend that expert opinion from social scientists trained in research ethics is required when reviewing and approving social and behavioural research.

**INTRODUCTION**

Social and behavioural research is a broad and multifaceted area that cuts across a wide range of disciplines, epistemologies and methodologies. Typical social and behavioural methodologies range from randomised clinical trials to ethnography and in-depth qualitative interviews. Social science research includes cross-sectional and longitudinal designs, examining the biological, psychological and social dimensions of human behaviour.

The requirement that social and behavioural science research be subjected to ethical review has been met with fierce resistance from some social scientists dating back to the early 1960s. (1, 2) Concerns from social and behavioural scientists focused on the utility and appropriateness of ethical review in these disciplines under the federal regulations for the current US Institutional Review Board or Research Ethics Committee (REC) system which is currently under revision for social sciences. (3) Because of some
resistance to ethical review of the social and behavioural sciences, this chapter will first discuss arguments against ethics review in the social sciences before outlining the critical areas that RECs reviewing social behavioural science protocols should concentrate on.

The arguments against ethics review of social and behavioural research can be divided into two broad categories: principled objections on one hand and pragmatic objections on the other. (4, 5) In the following section, we discuss these arguments to demonstrate that ethics review of the social sciences is not an unnecessary evil but rather a justifiable process intended to reduce the risks of harm to research participants, however small that risk might occasionally be. While all of the arguments must be confronted, it must be pointed out that many of them are based on opinion only and that there are relatively few empirical papers examining the attitudes and experiences of social scientists towards the ethics review process (6). The arguments thus only act as pointers to areas that need improvement in the way RECs should operate.

**PRINCIPLED ARGUMENTS AGAINST REC REVIEW, AND COUNTER-ARGUMENTS**

**Ethics review as a curtailment of academic freedom**

It has been argued that the imposition of ethical review on the social sciences might lead to curtailment of academic freedom as researchers might be deterred from presenting their protocols to RECs fearing disapproval. This argument can only hold water if academic freedom were to be viewed as the freedom to pursue any line of inquiry without due regard for the rights, safety and well-being of human participants. (5) In as much as academic freedom permits intellectual inquiry, it certainly prohibits the use of research designs and procedures that violate human rights and ethical standards. The well-being of a research participant takes precedence over all other interests. This argument is rooted in Kant’s categorical imperative which stipulates that every rational human being has intrinsic value and should be treated as an end and never as a means to an end. (7)

**Ethical universalism**

The three ethical principles of respect for personal autonomy, beneficence and justice are mistakenly widely regarded as universal and assumed to transcend traditional and cultural boundaries. (8) The blanket application of universal and so-called western ethical principles to all communities may thus be inappropriate, unfair, imperialistic and insufficient to address ethical issues in Africa and indeed other non-western countries. In view of the current debates on ethical universalism and moral relativism, it has been argued (9) that there should be a shift from viewing ethics as a set of universal principles to an understanding of ethics within a dialogic framework. International and
local moral codes of conduct should be critically evaluated at the point of application, for example, in the research communities where the research takes place. Macklin (1999) argues that ethical universals are not exception-less rules that are obligatory in all contexts. Instead, they are high-order principles that will generate different codes of conduct in each society. (9) It would therefore be a fruitless exercise to attempt to write “instruction manual” type directions declaring what is ethical or unethical in all situations at all times (10) based on the three principles. For this reason, scholarly work is being done to document African indigenous value systems so that their relevance to research ethics can be identified and implemented. (11)

Ethics review in the social sciences is derived from biomedical review

Some critics have argued that social and behavioural science research is reviewed using guidelines and systems of ethical review that were originally drafted with biomedical research in mind. (4, 5) Specifically, they argue that the guidelines were developed for and by biomedical researchers to protect research participants against physical harm mainly arising from medical experimentation (12) and may therefore be inadequate or irrelevant for reviewing social science research.

While it is true historically that a biomedical review framework was initially used for reviewing social and behavioural studies, it does not necessarily follow that social science protocols should be assessed using different moral standards than biomedical research. (5, 13) Rather, this argument only calls for pragmatic and institutional changes in the review system so that RECs focus on key ethical issues in social and behavioural science research as opposed to biomedical research. For this to be achieved, RECs reviewing social and behavioural science research should have at least one social scientist (trained in research ethics) on the committee. The issue is not about a biomedical framework being applied inappropriately to review social and behavioural science research but it is a question of having the right people to do the work using the best available frameworks. Competent ethics review of social science protocols requires that RECs have members competent in social science methodologies. (6)

Ethics review of social sciences is not necessary

It has been argued that social and behavioural science research carries far lower risk than biomedical research to the extent that it does not warrant ethics review. (2, 12) Related to this objection is the contention that the review of social science research endangers participants in high risk studies as the limited time and resources available for ethics review are diluted by the review of less risky studies from the social and behavioural sciences. (3, 14) If social and behavioural science research were to be exempted from ethics review, then more time and resources would be available for the review of more risky studies.
Admittedly, most social and behavioural research carries lower risks than biomedical research. However, social science research certainly poses concerns regarding voluntariness, threats to privacy and confidentiality and psychological distress — especially when answering sensitive questions — and stigmatization. While the risks posed by social and behavioural studies are generally low and different from some of those in biomedical research, this should not be a justification for precluding such studies from ethical review. In fact social science research should be subjected to more ethical scrutiny (4) considering that most such studies deliver fewer direct benefits to individual participants than biomedical research. (13) Additionally, the mere fact that there are risks of harm posed to research participants is sufficient grounds for ethics review. Considering that all researchers have a stake in the research projects they conduct, it is possible that they might deliberately or unwittingly ignore research risks in order to get participants enrolled and data captured.

PRAGMATIC CONCERNS

Social scientists have also raised concerns about practical issues related to ethics review. Among these are long turnaround times (4), incompetent review of the ethical and scientific aspects of social science protocols, inconsistencies between RECs (15), lack of capacity to monitor the study once approved (4), absence of specialised guidance on the review of qualitative research (8), to mention but a few. (6) These concerns in effect call for more explicit standards and procedures for the ethics review of social science research as well as for a common framework for decision-making when reviewing social and behavioural science research. RECs approving social and behavioural research should also be properly constituted with social and behavioural scientists trained in research ethics. Qualified members should be able to ascertain the value of the proposed study, potential systematic harms that may arise from the study findings (5), benefits that may accrue to study participants and communities by their participation in the study, including compensation for participation. Social scientists serving on RECs should not only have ethics training but the focus of their training should be on ethical issues in social science research. There is also a need to educate REC members about social science research methods and the risks they pose. (12)

The purpose of this chapter is not to accentuate the existing debates on ethical review in the social sciences, but to provide guidance to RECs on critical areas that need attention when reviewing, approving and monitoring social and behavioural science protocols in an African context. To review or not to review social science research should not be the question. We assert that the review of social science research is not only relevant but indeed necessary in view of several studies of questionable ethical standards that were conducted in the social sciences. Textbook examples of these studies include Philip Zimbardo’s Stanford Prison Experiment, the controversial Milgram studies on obedience to authority, Laud Humphreys’ ethnographic ‘tea room trade’ study, the
Wichita jury study (16) and the more recent scandal involving Dutch psychologist Diederik Stapel’s falsified work on race and stereotypes. (17) While these examples all come from developed countries, it would be naïve to assume that social and behavioural science research in developing countries has always been ethical. Efforts to compile data on unethical social science studies conducted in Africa should be undertaken in earnest.

**SPECIAL CONSIDERATIONS IN REVIEWING AND APPROVING BEHAVIOURAL AND SOCIAL SCIENCE RESEARCH**

Social science researchers encounter unique ethical challenges that warrant serious consideration. One of the key criteria used to review and approve protocols is to determine a satisfactory risk/benefit ratio, to ensure that the risks borne by participants are balanced by adequate benefits – both in relation to the knowledge that the study hopes to generate. Harm in biomedical or clinical research primarily includes physical harm while in the social sciences this includes non-physical harm in the form of emotional distress, stigma and other social harm such as destabilisation of social and relational systems, violation of privacy and confidentiality. The measurement of these non-physical harms, and in some cases, wrongs, is not easy and hence risk-benefit analysis in the social sciences can be quite problematic. More worrying is that relatively little guidance exists on the assessment of the ethical merits of social science research, in particular qualitative and survey research. (12) It may also be equally difficult to judge the social value of a proposed social science study especially when the REC members lack expertise in the field of study.

Most qualitative research is exploratory in nature and the focus of the study may change as a result of the interactions between the researcher and the interviewee. (8) In some cases qualitative researchers do not have the specific questions they intend to ask participants beforehand. Such designs make it difficult for an REC to review the study before its implementation. A challenge facing RECs reviewing social science research is that they cannot easily determine the probability and magnitude of harm, especially if the REC is predominantly biomedical in its membership. In a focus group discussion, for example, spontaneous personal disclosures may be made by participants even if they are briefed to discuss only general opinions on a specific topic. Further, it is not possible to guarantee confidentiality of personal information disclosed to other group members, even if all are encouraged to do so. In proxy surveys whereby researchers ask respondents about other people, or when dealing with hard-to-reach populations using a snowballing technique to recruit research participants, how are the rights of the third party or the person to whom the researcher is referred, protected?

Participatory action research (PAR), a form of qualitative social science research, requires a re-examination of the ethical obligations of risk assessment and the protection
of privacy and confidentiality in research settings. In PAR, the main objective is change and empowerment of participants and communities. In such studies, the physical, emotional and social harms associated with the research after its implementation should be considered together with the immediate or short term consequences. Such a task requires expert reviewers. Additionally, there are occasionally participants who might feel empowered if named as research participants and in the process this might strengthen the collaboration between the researchers and the communities and potentially mobilise social change. (5) Although it might be difficult to reconcile the primary objectives of PAR with ethical imperatives, it is not impossible (5), and is certainly not a case for discarding ethics review of such studies.

SPECIAL REVIEW CATEGORIES FOR SOCIAL SCIENCE RESEARCH

In view of the relatively low risk posed to research participants by most social science research, two standard review categories can accommodate many such studies, depending on local law and ethics guidance. Certain studies of social behaviour in the public domain (such as a study of pedestrian road safety behaviour) can either be exempt from ethical review or can be considered under expedited review procedures if minimal risk. It should be emphasised though that these are not the only two types of review categories that social and behavioural science protocols should be subjected to. Some social and behavioural studies might require full REC review because of the risks and other ethical considerations involved.

A FRAMEWORK FOR EVALUATING SOCIAL AND BEHAVIOURAL SCIENCE RESEARCH

The evaluation of research by RECs has largely been based on the three ethical principles of respect for persons, beneficence and justice as articulated in the Belmont Report. As discussed above, a major criticism levelled against the application of these principles is that they are abstract and regarded as universal; providing a basis for objective moral judgement across cultures and traditions. However, it has also been argued (18, 19) that a ‘Western’ value system, which forms the foundation of the principles, does not overlap fully with African value systems. The application and interpretation of these three principles in African contexts and indeed in most non-Western cultures is argued by some to create problems. (18, 19, 20)

Onuoha (20) developed an ethical framework which takes the African worldview into consideration. His framework is rooted in three main African values, namely humanity, community and morality — the key values that resonate with African worldviews, cultures and value systems. Considering that Africa has unique needs, Onuoha proposes three principles that are relevant for an African bioethics framework which
are: *respect for life, solidarity and justice*. While Onuoha’s principle-based framework is commendable, it is sad to note that it is yet to be operationalised in a way that will guide researchers and RECs in their normative application to social science (and other) studies.

Rather than focusing ethical evaluations on principles alone, concrete and practical guidelines for use when reviewing research proposals are desirable. One such framework, which embodies the three Belmont ethical principles and their practical implications, was developed by Emanuel, Wendler, and Grady (2008) and has been specifically adapted for social science research. (4, 5) Although the framework was developed with clinical research in developing countries in mind, we recommend the use of this framework by RECs evaluating social science research in Africa primarily because most social scientists will be familiar with the inherent values of the framework. The framework is based on eight principles namely: Collaborative Partnership, Social Value, Scientific Validity, Fair Subject Selection, Favourable Risk-Benefit Ratio, Independent Ethical Review, Informed Consent, and Ongoing Respect for Participants and Study Communities. The framework by Emanuel and colleagues will not be covered in detail in this chapter as it has been adapted for the social sciences and thoroughly described elsewhere. (4, 5)

**CONCLUSION**

The general composition of RECs should change. Those reviewing social and behavioural research should be experts in this field, supported by participant representatives where studies are high risk or require substantial participant engagement. (6) RECs should provide clear guidance on the types of studies that qualify for exempt and or expedited review in order to avoid unnecessary delays in the review and approval of research. Social scientists should themselves be systematically trained in the ethical aspects of their research to protect the welfare of their research participants and hence also receive more favourable ethics reviews.

**REFERENCES**


INTRODUCTION

Recent technological advancements in the field of genetics and molecular biology have led to an increase in the number of genetic and genomic research projects in Africa. (1, 2, 3, 4) Genetic research aims at understanding a specific gene or genes, and their relationship with disease conditions, in particular inherited traits, whereas genomic research focuses on the entire genome of an organism. The study of genetics may, for example, assist in understanding how a particular gene or genes contribute to disease susceptibility. Genomic research, in contrast, due to its much greater complexity, involves more sophisticated analysis. An example of such research is genome-wide association studies (GWAS), which involves ‘scanning specific genetic markers across the entire genome of multiple people to identify genetic variations associated with the disease’ (www.genome.org). It is important that the distinction between genetics and genomics is made during the review process, since the practical ethical issues that are involved might not be similar. (1) Also, not all the members of RECs, nor potential research participants, will be familiar with many of the scientific processes involved in genetic studies. The need for conducting both a scientific review and an ethics review...
is, therefore, clear. Research ethics committees should determine whether a proposed genetic and genomic study has received scientific approval, what issues are to be raised in the study, and how the issues are to be addressed.

Since the Human Genome project in 2002, there has been a steady rise in the number of international collaborative projects on genetic and genomic research taking place across the globe. Recent advances in molecular genetics, computer technology and high-throughput DNA sequencing have also resulted in an increase in the establishment of international scientific networks and collaborations. Examples of the above include the Malaria Genomic Epidemiology Network (www.malariagen.net), and, recently, the Human Heredity and Health in Africa Initiative (www.h3africa.org). In many cases, genomic research, particularly in the context of collaborative research, involves the collection, storage, export and sharing of samples and associated data across national borders and continents. (5, 6, 7) Such research raises concerns about the ownership and the control of samples of the scientific resources involved.

The scientific justifications for conducting genetic and genomic research in Africa, which are numerous, have been discussed extensively in the literature (see comprehensive report on Genomics and World Health: report of the Advisory Committee on Health Research, 2003). (8) They include the opportunities for African scientists to address unmet health needs, to conduct future research with archived samples, and to reduce research costs.

However, such developments also bring with them new ethical challenges, which have implications for the ethics review process. In the next section of this chapter, we explore some of the key ethical issues arising from genetic and genomic studies in Africa, as well as from other studies involving human biological samples. The focus of the section is on the literature from sub-Saharan Africa, including empirical research studies and own experiences, in order to highlight the unique ethical challenges that are relevant to research contexts in Africa.

**ETHICAL ISSUES ARISING IN GENETIC AND GENOMIC RESEARCH**

The collection, storage, export and potential future uses of human biological samples, particularly in genetic and genomic studies, present a number of ethical issues that research ethics committees (RECs) must take into consideration in the review process. Such issues include consent, community engagement, privacy, confidentiality, data sharing, capacity building and benefit sharing.
VALID CONSENT

A key ethical issue is seeking valid consent in genetic and genomic research. Several ethics guidelines, such as those of the Council for International Organizations of Medical Sciences (9) and the Declaration of Helsinki, (10) have stipulated that, in order for consent to be valid, it must be informed, voluntary, and given by a competent person. Empirical studies in Africa have highlighted several challenges regarding the nature of valid consent in the case of genetic and genomic research. (11, 12) Said challenges include the lack of understanding of scientific aspects of research, difficulties in finding appropriate terminology, and the lack of concepts in the local languages for such scientific terms as ‘genes’, ‘genomes’, and ‘database’. Despite the above-mentioned challenges, obtaining valid consent for genetic and genomic research is, nevertheless, possible within the African context. In the review process REC members should ensure that consent form information covers all the important aspects of the research, including the purpose, the procedures, the anticipated risks, and the benefits, as well as the upholding of confidentiality. Additional information that is required includes such issues as who may have access to the genetic information, whether there are any plans for patenting any genetic material, and how incidental findings are to be handled or managed. The information in question should be presented in clear and understandable language. The use of analogies and analogies, illustrations and pictographs is helpful in explaining scientific concepts so as to improve research-related understanding.

Another consent-related issue is the unknown nature of the future uses of stored biological samples, with the information concerned being required to be provided to prospective participants. (3) Broad consent, in terms of which the participants involved consent prospectively to broad future uses of their samples, is the current practice. Recent empirical studies in Africa indicate that participants are generally supportive of providing broad consent for future uses of samples, (13) on condition that it is for a ‘good cause’, (14) and appropriate measures are in place to prevent unethical research practices. (3, 15) This means that RECs should provide effective oversight for future uses of research samples, with periodic updates from researchers and research institutions regarding the status of stored and exported research samples, as well as determining whether or not a proposed future research project is justified.

Community engagement

Community engagement is important to ensure the protection of participants, for building a trust relationship between researchers and the community, and to address the ethical issues arising from genetic and genomic research. (11, 16, 17, 18) However, the questions relating to what constitutes effective community engagement and how local communities should be engaged around the use of human biological samples remain unanswered. There are several examples from Africa on how communities can
be engaged effectively in such an exercise, such as by means of organising community meetings, consulting community leaders, and working with community advisory boards. (17, 19, 20) For genetic and genomic research, which has implications not just for individual participants, but for families, communities and entire populations, community engagement should be a recommended practice. It is particularly important for RECs to assess the processes that research projects will utilise in engaging communities in research in order to address any community concerns. Doing so will require assessing how the community is defined in terms of the research, and what kind of engagement is set to take place.

Privacy and confidentiality
The information that is generated from genetic research has the potential to harm research participants, in that it can lead to discrimination, stigmatisation, and the possibility of revealing false paternity. It is, therefore, recommended that RECs assess what measures are in place to ensure the privacy of the providers of genetic information and confidentiality of such information. Researchers should also disclose in advance who will have access to what information, under what circumstances, and to whom. Quality control and assurance measures should be documented to ensure the maintenance of security and confidentiality during the sample collection, storage, handling, and distribution, as well as during the destruction of the samples and the preservation of data.

One approach that can be taken to prevent unintended harm is to ensure anonymity in the storage of samples and/or data. The REC concerned should, therefore, use its discretion when assessing the secondary use of genetic data, in terms of the safeguards provided by the investigator that are aimed at preserving the confidentiality of research participants, and, by extension, the communities that they represent.

Cultural sensitivities regarding human biological samples
Most genetic and genomic research depend on access to large numbers of human biological samples, such as cells, tissues, organs, blood, and DNA. Literature from Africa suggests that there are often tensions between medical researchers and communities regarding the use of blood samples in biomedical research in general. (3, 21, 22) Empirical studies have also suggested that, whereas most communities across the continent appreciate the benefits that they derive from participating in research activities, there is the perception that their blood or tissue is stolen from them. For example, Fairhead and Leach report that Gambian participants view the Medical Research Council (MRC) as an institution that ‘offers good, free medication to participants, but also steals blood’. (23) Molyneux et al. have also highlighted a range of concerns expressed by local communities in coastal Kenya about blood taking, including ‘not understanding what the blood is for and concerns that the blood will be used in “other things”’ (such as being
sold for profit). (21, 24) Some of the rumours could be blamed on the lack of adequate information provided, or on misinformation regarding the purpose of blood sampling in research. These perceptions should be addressed during instances of community engagement.

However, it is important to recognise that local rumours have implications for genetic and genomic research, and that they could potentially undermine the viability of important research projects in Africa if they are not addressed. (25) RECs should assess whether the sample collection process used is culturally appropriate, what the local concerns regarding sample use are, and how they will be addressed. The REC should determine what the most appropriate biological sample would be from which to answer the proposed research question.

Benefit sharing

Benefit sharing is one of the key ethical issues arising from genetic and genomic research, especially in the context of international collaborative research. Given the potential profits that are possibly derived from discoveries made from human biological samples, questions remain about how the benefits should be shared between the stakeholders involved in designing and carrying out the research, ranging from sponsors and the researchers, to participants and the communities. (26, 27) Some scholars have advocated for an equitable distribution of the potential benefits of research. (26, 27, 28) However, what benefits should be shared, and what counts as ‘fair’ in the distribution, can be very complex to determine. Depending on the nature of the research collaboration, research benefits can range from free access to health care, through reimbursements for transport costs, to infrastructural development. (29, 30) The REC concerned should ensure that the research is not exploitive in Africa, and that adequate provisions have been made for an equitable distribution of any benefits that might arise from the studies involved. Doing so involves assessing the relevance of the research to the local population, as well as the benefits of the proposed research, the potential patent rights, and whether the data will be shared with for-profit companies.

Sample export and data sharing

In the context of international collaborative research, research samples are often exported and stored in well-established laboratories in the developed countries. (2, 5) There is also an increasing drive from the sponsors and the funders of research to make the data generated from research widely available to the research community. The scientific justifications for sample export include the lack of local capacity for sample analysis, the requirements that are set for uniformed analysis in multicentre trials, and the contributions that are made to international research consortia or research networks. What is not clear is whether making information about sample exports
known is a necessary requirement for valid consent, and, if so, how such information should be shared with potential participants in the research concerned. (3)

Research participants have the right to information about the possibility of, and the justification for, sample exports, as well as for subsequent data sharing. The recommendation is that RECs should assess whether the relevant information will be provided during the consent process, and that measures should be in place to ensure that exported samples are used only for approved research. A key recommendation should be that material transfer agreements between the host institution and the collaborating institution are in place to protect the interests of research participants and local researchers. Additionally, the REC should ensure that participants are informed about the possibility that their samples and the associated data will be accessible to third parties.

Capacity building

Another emerging challenge is the lack of adequate personnel and infrastructural capacity in Sub-Saharan Africa (SSA) research institutions for conducting genetic and genomic studies. RECs should assess the capacity of local personnel and infrastructure to see whether they are adequate for the carrying out the proposed research. The assessment should take into consideration any capacity-building plans as part of the research project concerned, particularly in the context of international collaborative research.

Provision of feedback regarding research findings to research participants and communities

The provision of feedback about the research results obtained is another ethical issue that should be assessed during the review process. In genetic research, supplying feedback on research findings might be necessary if there are potential health benefits to be derived from the findings by the participants concerned. In the case of genomic research, however, giving feedback on research findings might not be feasible. It is, therefore, important for RECs to assess when and how the results of genetic and genomic studies should be shared with the research participants and the communities involved. Such assessment should include all due consideration of the dissemination plans of the results of the proposed research, including the sharing of information with individual participants, and under what conditions such sharing should take place.

**KEY ISSUES TO CONSIDER DURING THE REVIEW PROCESS**

During the review process, the following key issues require consideration.
1. General relevance and social value of the proposed research

In terms of the general relevance and the social value of the proposed research, the following questions should be asked:

- What is the scientific justification for the proposed study?
- What are the potential risks and benefits of the study?
- What are the recruitment procedures and the eligibility criteria concerned?
- How appropriate is the choice of population from which the study participants will be drawn?
- What are the risks of the genetic analysis?
- What measures are in place to ensure the appropriate contextualisation of study results, in order to make them understandable to the research participants?
- Will genetic counselling be available if the participants experience distress or anxiety when receiving the study results?
- Does the research team have the necessary expertise, as can be determined by checking their curriculum vitae, to inform the potential research participants about the risks and benefits of the study?
- Will the genetic information be documented in a medical record?

2. Plans for the collection and analysis of human biological samples

a) Collection of samples

Regarding the collection of samples, the following questions should be asked:

- What type of samples will be collected – blood, serum, tissue, or DNA?
- What is the amount or size of the tissue to be collected?
- What is the justification for collecting the samples?
- What procedures (e.g. venipuncture) will be used to obtain the samples?
- Is information about the intended sample collection process provided in the consent forms?

b) Analysis of samples

Regarding the analysis of samples, the following questions should be asked:

- What type of analysis will be undertaken?
- Where will the analysis be done (locally or outside the country)?
- What are the potential risks and the known nature of such risks related to the proposed genetic research? How will the risks concerned be minimised? Is there a possibility of stigmatization or any social harm?
- What will happen to biological samples after the analysis? Will they be used again, destroyed, or stored for future use?

c) Plans for biological sample export

Regarding the plans for biological sample export, the following questions should be asked:

- Are the justifications for sample export:
  - the lack of local human resource capacity or equipment;
  - the need for a uniform analysis (in the case of multicentre trials), or
  - making a contribution to a research consortium?
Is the information on sample export provided in the consent forms?
To which destinations will the samples be exported?
Who will be responsible for the control of the exported samples from third party or tertiary use?
What agreements have been reached for sample export? Is a material transfer agreement (MTA) in place?

d) **Plans for the storage of samples and associated data**

Regarding the plans for the storage of samples and associated data, the following questions should be asked:

- What type of sample will be stored?
- What is the rationale for sample storage:
  - planned future-related research;
  - anticipated future-related research;
  - unanticipated future-related research, or
  - unanticipated future-unrelated research?
- Where will the samples be stored? Will the storage be local, national, or in an international repository or biobank?
  - What is the justification for storing the samples outside the host institution?
- For how long will the samples be stored?
- Who will have primary control over the samples?
- Is information about sample storage included in the consent form?
  - An example of the wording that could be used in a consent form is *I agree that my samples may be stored in . . . (location of samples storage).*

e) **Sample and data sharing**

Regarding sample and data sharing, the following questions should be asked:

- Have provisions been made for access to, and ownership of, genetic information, findings or products?
- Will identifiable data be accessible, and how will confidentiality be maintained?
- How will the DNA/RNA sample/storage be handled? Will the researchers be likely to contact the participants for additional samples?
- What procedures should the study participants use to request that their sample/cell line be destroyed or stripped of identifiers (keeping in mind that the way in which genetic material will be coded should be documented)?
- Will genetic material remain coded and anonymous (noting that, at times, keeping the material in this way might render future research difficult)?
- Will the samples or information gained be shared with third parties? If so, will such sharing be done in an anonymous manner, using coding?
- Will the benefits of the research be shared with the community in which the research is conducted?
- What will the implications be of disclosing the results of the findings to the research participants or to their representatives on their request, or if doing so is part of the
clinical care provided for the individuals concerned? If the results will be shared with the research participants, or with others, the following points should be considered:

− how the research participants would be likely to benefit from the research results;
− how predictive the tests would be likely to be of the condition, disease, or genetic trait involved, and
− whether the testing would be available outside the research context.

CONCLUSION

Genetic and genomic research offer important research opportunities for addressing unmet health needs in Africa, with a key way of doing so being through collaborative research. In the current chapter, we have highlighted the key ethical issues that are likely to arise in genetic and genomic research, as well as their implications for the participants in such research, and their communities. Given the plethora of guidelines currently governing research across the globe, it is important for RECs in Africa to take into account the unique challenges that are likely to arise within the field of genetic and genomic research in Africa. The contents of the present chapter are based on existing guidelines, on African empirical studies, and on personal experiences of summarising the key points that should be made in this regard.

REFERENCES


18

Payment of Research Participants

Khama Mita, Paul Ndebele

Key Message: Payments that are made to research participants for reimbursement of costs associated with research participation, or as incentives aimed at encouraging enrolment or continued participation.

Introduction

Paying research participants in cash or in kind to participate in medical experimentation can be traced as far back as the gut experiments of William Beaumont during the 1820s and the yellow fever experiments of Walter Reed in the year 1900. (1) Financial incentives are proposed or used by individual researchers or by research institutions to enable the recruitment and retention of individuals as participants in research. (1) Most current research ethics regulations and guidelines allow payments to be made to research participants, but provide little instruction regarding the appropriate rates, and what they should be for. (2, 3) Most organisations, including research-funding agencies, make allowance for some payment to be made to research participants, but few have written policies on the making of such payments. (4) Because investigators and research ethics committees (RECs) make payment decisions with little specific guidance, standards of payment vary. The topic of financial incentives for research participants is problematic for RECs, researchers, research sponsors, and for the field of bioethics as a whole, because of the fear that financial incentives may unduly influence the decisions of prospective or current research participants regarding participation in clinical trials.

First, there is a need to clarify certain terminology when dealing with the topic of research participant payment. The terms that require a clear definition for them to be appropriately understood in the context of the present chapter are ‘inducement’, ‘undue influence’, ‘coercion’, and ‘incentive’.

- *Inducement* is the act whereby someone is enticed or persuaded to take a certain course of action, whereas ‘compensation’ refers to the remuneration and other benefits that are received in return for services rendered. (5)
The improper use of trust or power is likely to exert *undue influence* in a way that deprives a person of free will and/or that substitutes another’s objective in its place.

_Coercion_ is the act of compelling by force of authority. (6) It is of utmost ethical importance that subjects should not be coerced into participating in a study, and that they should be able to choose to participate freely, voluntarily, willingly, without duress, and with no threat, or an excessive reward promise. (6)

_Incentive_ is a drive that motivates or encourages someone to act in a certain way, or to increase their effort in a certain direction.

From the above definitions, it is evident that incentives or inducements are not, in and of themselves, bad phenomena. They only become bad when they encourage individuals to make decisions that they would not have made if they had not been present.

Two ethical principles of bioethics are considered to be relevant when one looks at the issue of financial incentives, namely justice and autonomy (which is also referred to as ‘respect for persons’). The following points need to be borne in mind in relation to these principles:

- **Justice** refers to the ethical obligation to give to each person what is due to him or her. Payments should be fair in distribution and to those who deserve them. Accordingly, this distributive justice refers to what ought to be given to individuals for the burden that they bear.

- The second ethical principle that is raised in relation to financial incentives is that of **autonomy**. When they are provided with financial incentives, individuals might make decisions that they would otherwise not have made. According to Beauchamp and Childress, all theories of autonomy agree that each person should possess the liberty in decision-making that is independent from controlling influences if the person concerned has the ability to perform intentional action. (7)

Five proposed models are suggested for the payment of research participants, namely the market model, the wage payment model, the reimbursement model, the appreciation model, and the fair share model. (8) The models are outlined below:

- The **market model** uses the forces of supply and demand to determine how much a participant is paid.

- The **wage model** uses the premise that research participation is similar to unskilled labour hence research participants are paid amounts that are similar to the minimum wage in the country in which the study takes place.

- The **reimbursement model** envisages research participants as requiring repayment for their actual costs incurred due to their participation in the study, whereas the **appreciation model** considers that participants should receive financial recompense in the form of rewards or tokens of appreciation for their participation in a study.

- Other authors favour the **fair share model**, in which research participants are paid an amount that is deemed to be fair. (9)

The topic of financial incentives being given to research participants troubles RECs, researchers, research sponsors, and those who are involved in the field of bioethics for
various reasons. Whereas payments might be used to encourage the participation of human subjects in research, they might also, unfortunately, ultimately serve as undue inducements. The Belmont report states that inducements that would ordinarily be acceptable might come to be regarded as undue influence if the subject involved is especially vulnerable to such inducements. (10) Undue influence tends to occur if the offer is inappropriate or improper or due to an effort to obtain compliance with a specific research regimen. (10) The major focus of inducements has, in the past, been on financial incentives. Concern has been expressed that such financial inducements decrease the ability of research participants to volunteer to take part in research, thus nullifying the entire concept of valid consent. Although financial inducements act as controlling influences, it is difficult to decide the cut-off point at which they become undue influence. Vulnerable populations, according to the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, are those participants who may unwilling volunteer for a clinical trial due to undue influence of expectation or fear of retaliation by a senior member in the hierarchy if they should refuse participation. (11) International guidelines for the ethical conduct of research do not adequately address the issue of financial incentives, hence the ability by different investigators to make payments of varying amounts of money.

Incentives in biomedical research have, over the years, become acceptable practice, even though no guidelines are yet available as to how they should be calculated. Currently, researchers tend to award study participants financial incentives either for recruitment or retention purposes, with said incentives varying in amount from country to country, and from researcher to researcher. Some countries have devised guidelines recommending the acceptable amounts that participants should be paid. Although setting such national levels might be viewed as being a positive step, doing so supports neither those studies that are self-funded, nor those that are funded by local organisations that lack the capacity to provide sufficient funding to cover the payments that they are required to make, in terms of such guidelines, to the participants concerned. As a result, locally funded studies might suffer. Some research institutions have also devised what is known as a standard rate for financial incentive, whereas others stipulate no such rate, thereby creating variations within the institution itself. The institutional rate might also disadvantage institutions without a standard rate, as individuals are only likely to volunteer to participate in studies where they are guaranteed of payment.

The National Health Research Ethics Council (NHREC) of South Africa has recently approved a guidance document for the payment of trial participants which recommends that trial participants should be compensated for time at the national hourly rate recommended for unskilled labourers, may be compensated for inconvenience and should be reimbursed for expenses. (12)

So far, RECs have played mainly a regulatory role in relation to the offering of financial incentives to research participants. The RECs have determined whether the financial
incentives offered are ethical or not, with such determination being made in the absence of guiding principles as to which incentives are ethical or not. Different methods of determining possible offerings have been used. The Council for International Organisations of Medical Sciences (CIOMS) guideline 7 addresses issues of inducement to participate and deals with some of the scenarios where inducements may be used and in what form, whether as compensation, payments or reimbursements. (3) In terms of the guideline, what criteria are to be used to approve the allocation of said amounts are to be based on the fact that the participants concerned are not induced to participate in the study against their better judgement.

Monetary payments have had positive effects on recruiting participants into research, with such effects being independent of the level of risk involved, according to Bentley et al. (5) Another study, which was conducted by Dickert et al., found that, although most organisations pay research subjects, few have written policies on the making of such payments. (4) Poor participants are influenced even more strongly than are wealthier ones, which raises additional concerns regarding research targeting low-income participants. (13) The concern is not whether to pay subjects or not, but, rather, how to decide what to pay in order to rule out any chance of exploitation or coercion. A concept that is introduced in such a context is that of exploitation. Exploiting people means taking unfair advantage of them. (9) The ethics guidelines for RECs indicate that the level of payment should not be so high as to amount to it serving as an undue inducement. The REC should review both the amount, as well as the timing, of the payment to be made, in order to ensure that there is no coercion or undue inducement.

Macklin insists that RECs should examine both the recruitment practices and the payment amounts rendered to normal healthy volunteers, as well as ensure that consent is obtained without deceit, force, fraud, or duress, and so that there is no undue inducement involved. (14) A special emphasis should also be placed on protecting vulnerable populations, as is described in the ICH GCP guideline referred to above. Rice et al. discuss ethical issues related to the use of incentives with children, in connection to which they suggest that deciding appropriately on the type and amount of the incentive requires knowledge of the context and of the local practice concerning research with such a population. (15) An underlying concern is that vulnerable persons can be influenced by incentives that might place them at greater risk than usual because they wish to obtain the goods or services offered by the researchers. (5, 6)

The amount of talk that revolves around the issue of undue inducement in clinical research has led some authors to feel that the concern expressed is misplaced. Emmanuel, in his article ‘Ending Concerns about Undue Inducement’, argues that undue inducement is not, actually, the major concern in the debate regarding the issue of the payment of participants in research. According to Emmanuel, the real problem lies in how to ensure that prospective participants are not enrolled for excessively painful or risky research trials. To him, the cornerstone is good independent ethics review, which should help to
ensure that any trial that is undertaken fulfils all ethical requirements, and does not pose excessive risks to the participant involved, who might have been induced to participate in the research concerned due to skewed judgement resulting from the high incentive offered. (16) This argument disregards the fact that not all RECs in Africa are competent to make judgements on risk–benefit ratios. Inexperienced RECs may not be in a position to provide maximum levels of protection, due to weaknesses in their review processes. In a world that is dominated by the profit factor, risky trials tend to be channelled to countries with weak human research protection systems, where poverty increases the likelihood of prospective participants signing up for even a high-risk study.

The principle of justice is another issue for concern, as the financial incentives that are on offer can result in participants involving themselves in activities bearing greater risk than the concomitant benefits from which they stand to gain as a result of their participation in the research concerned. The form of injustice that is involved in such instances is of a social nature. Ballantyne argues that financial inducements do not distort research participants’ assessment of risks, but, rather, that investigators should focus on awarding fair benefits to the participating subjects. (17) She has expressed a belief that research subjects are exploited when they are paid too little. It is suggested that, especially in the context of international research, in cases where the financial payments that are made to research participants are deemed to be excessive, part of the payments should be converted into non-cash goods or into community benefits, so as to reduce the amount of undue influence that might otherwise be exerted on the research subjects concerned. (18) In addition to the above arguments, other researchers assert that, in limited resource settings, local leaders should be involved in determining, from the outset, the rewards that are to be due to the study participants, as well as to the whole community in which they reside, within the limits of the study budget. (18)

Some confusion pertains to the terminology that is used with regard to whether paying participants amounts to reimbursement, incentive or inducement, although there is evidence that the financial payments that are being made to research participants, however they may be regarded, are determined by means of certain specified methods. One such method entails the payment of the transport costs of subjects to and from the research clinic concerned, to enable them to continue participating in the research study. Much literature covers the use of incentives in biomedical research, although certain gaps still exist as the researchers concerned are not clear on how to implement such practice. International guidelines tend to be more explicit on how to handle the issue of financial incentives in biomedical research.

**CONCLUSION**

Ethical issues surround the practice of providing financial incentives in health research, since there are no written guidelines to clarify such matters. Countries, institutions,
sponsors and researchers make decisions regarding payment levels based on various factors. As a result, there are variations in payments across nations, organisations, sites and studies. The REC’s role is to determine whether the offers that are made are appropriate and locally acceptable. The RECs find it difficult to make judgements in this regard, due to the varying settings involved, and also due to the fact that no written guidelines exist that can be used to help determine which amounts are appropriate. Consequently, the following practical recommendations deserve due consideration:

1. Researchers and RECs need to consider the local context when deciding about financial payments for participants.
2. RECs should decide which payment model(s) are appropriate for a particular study.
3. The RECs need to review and approve all forms of payments, including gifts, in order to ensure that they are appropriate and acceptable.
4. In terms of the relationship between risk and payment, if the research involved is very low risk, then concerns regarding ‘persuasion or inducement’ are less relevant. Considerations about payment become more critical with high risk studies such as certain placebo-controlled trials.
5. Researchers and RECs need to strike a balance between avoiding the exploitation of research participants by making excessive payments to individuals and communities and exploitation of participants by using participants without compensating them for their time, effort and pain.
6. RECs should encourage researchers to convert some monetary payments into health-promoting items or benefits, so that study participants will directly benefit from their participation in a study.
7. Where RECS feel that the payment involved is excessive, they can recommend that part thereof be converted into non-cash goods, or other forms of community or individual benefits.

REFERENCES

INTRODUCTION

The definition of the term ‘community’ is problematic, since communities are not homogenous entities. Use of the term may refer to a neighbourhood, city, county, or other geographical area that is made up of many different groups, who think of themselves as communities. Such use can also refer to a number of groups with common interests, but that do not share a common geographic location. Although a community is defined by at least one commonly-shared characteristic, individuals and groups comprising a community may also be diverse in respect of their socio-economic status, religious affiliation, race, or ethnicity. Despite the fluid nature of the term, community engagement activities in research studies are predicated on the definition of the term ‘community’ that is employed by particular research studies. A functional definition of a community is “groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the well-being of those people”. (1)

A research ethics committee (REC) should ensure that the prime goals of community engagement are to establish a trust relationship and to facilitate communication between researchers and communities. Successful community engagement can improve overall health outcomes and build lasting collaborations. Promoting research ethics through partnerships between communities and RECs, and ensuring community perspectives in REC review processes, tends to build greater respect between RECs and communities than might else exist. (1, 2, 3)
ETHICAL PRINCIPLES AND COMMUNITY

The principle of respect for persons requires the treatment of individuals as autonomous agents, who are capable of making their own independent decisions regarding their personal goals and choices. (4) However, some research projects (namely, those that are population-based, or that are concerned with issues of public health) target entire communities rather than individuals, and the conventional methods that are usually used for obtaining consent might have to be modified in such research. Consequently, expressing respect for the community assumes particular significance, as much as does showing respect for persons in clinical trials that randomise individuals. The principle of ‘respect for community’ may be discharged by consulting recognised community leaders or established community structures, with those concerned consisting of individuals, groups or community-based organisations (CBOs). (5) Community consultation and communication should be an ongoing activity that enables the expression of a sustained ‘respect for community’.

Beneficence refers to ‘the moral obligation to act for the benefit of others’. (6) People become benevolent when they act for the benefit of others. The goal of community health research is to produce knowledge that is beneficial to the community, and the researchers should possess the necessary qualifications and skills to conduct such research. Researchers should ensure that their research participants are protected from harm. Whereas the obligation that researchers have towards individual participants regarding the prevention and minimisation of risks and harm is well-documented, little attention has, so far, been focused on preventing risks and harm to the community. Researchers must recognise and appreciate that risks to the general community (community members that did not participate in the study) do exist. (7) For example, an entire community that participated in a research project might become subject to risk if the results of a research project are misinterpreted. (8) Other potential negative impacts that might result from research could involve the recruitment of critical health staff for the research process, depleting the work force in routine health care. (9)

Justice is a particularly important principle in the context of community engagement, which requires that related benefits and burdens should be fairly distributed among all groups in the community concerned, without allowing such issues as age, gender, culture ethnicity, and socio-economic status to influence distribution unduly. Research should not deliberately target vulnerable groups in the community. All research, with the potential to cause psychological, social or physical risk to individuals, communities or groups within the community, must be critically evaluated for the likelihood of such risk. (4)

THE ROLE AND RESPONSIBILITY OF THE RESEARCHER IN COMMUNITY ENGAGEMENT

Community engagement or community participation has become a significant feature of research studies, and, in particular, of clinical trials. Various terms are used to describe
research entailing community participation, such as action research, participatory research (10, 11), cooperative enquiry, participatory evaluation, and community-based participatory research (CBPR). (11, 12) Participatory research involves the community collaboratively in the entire research process. Such research enables lay and local people, or those who may be termed ‘non-academic researchers’ to participate actively in knowledge creation (12), while simultaneously, the fully-fledged researchers concerned become more aware of the lived experiences of those on the ground. (7, 13, 14)

Several authors have outlined the process that is undertaken in engaging the community. (15) In the following discussion, we base our thinking on Hatch et al.’s process of community engagement, (16) while, simultaneously, drawing on the experience of others in the field. According to Hatch et al., there are three different levels of community engagement: consultation, collaboration, and partnership.

**Community consultation:** As with any other process, community engagement has, first, to be initiated, whereafter the researchers engage the community in a relationship, starting with involving it in building activities during the consultation stage. (17) Involving the community in the process at an early stage might impact positively on the future partnerships between the researchers and the community concerned. (18) During the research process, the community consultation can take the form of formative research, which helps the researchers to gain a deep understanding/knowledge of the local community with which they intend to work. (19) Keeping in mind that communities are living entities, with different socio-cultural norms, power dynamics and decision-making mechanisms that impact differently on the conduct of research, formative research can generate information about community characteristics and their potential influence on research. For example, in the context of HIV prevention research, formative research might be instituted to enable the rapid assessment of the HIV risk behaviour in the host communities to identify the catalysts and barriers that could influence the uptake of the research intervention. (20) If, at the consultation stage, researchers lack in-depth knowledge about the community, consultation with the latter could provide the basis for gauging and improving the socio-cultural competency of the researchers concerned.

Community consultation, when it takes the form of formative research, can lead to community participation in protocol development, albeit indirectly, if the consultation is conducted before the research protocol or proposal has been finalised and submitted to the relevant authorities for approval. Findings from the formative research might turn out to provide useful community perspectives that ensure that the research project will be relevant to the community and that the knowledge and experience of the community are respected. (18) Community consultation might also enhance the protection of communities in research projects if the results of the consultation process identify potential community-level risks. However, community representatives’ involvement in planning and in informing the community of the research study is currently limited. (19)
**Community collaboration:** Community ‘consent’ (referring to the endorsement of the research project concerned by community bodies) is said to only be possible in those situations where a legitimate political authority is in place. (21) In the African setting, the legitimate authority might include chiefs, village headmen, tribal councils, political representatives (especially of whatever party is in the government), and government-backed development and health-related community-based organisations that make choices for the community. In the absence of such bodies, community support might be obtained from other community stakeholders. The moral standing of such ‘consent’ may still be of worth, provided that the process that is undertaken is both inclusive and democratic. Community-based research requires community leaders to endorse a project and provide guidance in hiring community residents to serve as interviewers, outreach workers, and facilitators, which is different from community-engaged research, which refers to research where community members are involved in the design of the research project. Community-based research could potentially lead to manipulation if research teams are persuaded to hire influential community members. (16)

One way of ensuring inclusiveness in both community consultation and consent is to undertake a stakeholder analysis. Such an analysis might be conducted independently, or as a follow-on activity to the formative research. Community stakeholders are groups, CBOs, individuals, and government, as well as non-governmental, organisations that can influence, or that might be influenced by the implementation or by the results of a research project. (19) For example, in HIV and related research, use of the following questions might help to identify the community stakeholders concerned:

1. Which groups and organisations are currently dealing with the health condition being researched?
2. Which groups and organisations provide care and support for the sick?
3. Which organisations or individuals are often consulted in healthcare-related decisions?
4. Who are considered to be the opinion leaders in the community?
5. Which groups and individuals are generally left out of healthcare decision-making?

Answers to the questions above can be used to identify the appropriate stakeholders to consult for community consent and/or for advice during the implementation of the research project. It is important to note that non-public authorities (or bodies) might also have a role to play in obtaining community consent, or in communal decision-making. (22) As a consequence, the stakeholder analysis should be broadened to include as many relevant stakeholders as possible. Similar to the situation that prevails with obtaining informed consent, community consultation is an on-going process. However, initial consultation, before the commencement of the research project, is particularly important for the following reasons:

1. It enables the researchers concerned to gather diverse community perspectives that improve their understanding of the community.
2. It provides researchers with an early advantage regarding which engagement and community advisory mechanisms to put in place, and what their possible composition could be.

3. It enables researchers to gain insight into the possible power dynamics among the various community stakeholders involved. Sometimes, researchers might choose bodies or groups that are not representative of the community to participate in a study. (10) Members of bodies like the community advisory boards (CABs) might have personal interests or agendas that present a challenge to researchers who seek to identify those with a genuine interest in representing the community. (7)

**Community partnership:** Researchers must consider community members as partners when identifying the health challenges to investigate, when coming up with the research idea and when proposing possible solutions. (16) In research projects, CABs provide a realistic way of helping to ensure the integrity of such a partnership. The history of CABs, itself, reflects a struggle for the building of partnerships. The advent of AIDS drug and vaccine trials catalysed the birth and growth of CABs. As the need for an effective treatment for the pandemic gathered momentum, activists began to exert pressure on the researchers involved, and started to demand a bigger role in determining research agendas and priorities and participation in the study design and drug development and approval process. (7) They also advocated that the community be included in the trial process. Later Tenofovir trials in Cambodia, Cameroon and Nigeria were stopped, as the activists objected to, among other things, the lack of community participation in the trial design. (23) The pressure of such calls was heightened when it was discovered that participants in the randomised clinical controlled trial of azidothymidine shared their doses to ensure that all participants had access to the experimental drug, especially for those on placebo. (24) The consistent efforts exerted by activists eventually paid off when a community constituency group, which was composed of community representatives from various research sites across the United States, was created within the National Institute of Allergy and Infectious Diseases (NIAID). Said move was followed by the formulation of policy guidelines that were instituted by NIAID. The guidelines required that all the clinical research sites that were funded by NIAID should establish CABs, thus extending the concept to international settings. (25)

CABs are organised groups of volunteers who are appointed or elected by community members to represent them in research studies. (17) CAB members, who are usually residents of the community that they represent (26), tend to come from different backgrounds and disciplines. Among them can be found: former study participants; retired civil servants; serving civil servants; people living with HIV (PLWH); treatment and human rights activists; professionals working in schools and non-governmental organisations, and representatives of the media. (26) The size of the CAB usually ranges from 10 to 15 members, which is an ideal group size for attaining, and also for managing, meaningful interactions between members.
If they are well utilised, CABs can enrich the informed consent process and enable the protection of the research participants’ interests by enhancing the partnership between the researchers and the community. (27) CABs also improve the consent process by facilitating the communication of the goals, benefits and risks of the study to the community to enable the latter to make informed decisions regarding their participation in the study. (10)

In situations where they have been successfully established, the existence of CABs improved relations with the community, as well as facilitated the study subject recruitment. (28)

**THE ROLE AND RESPONSIBILITY OF THE REC IN COMMUNITY ENGAGEMENT**

The REC must answer several important questions during the research review process, namely:

- Has the study clearly defined both the research and the broader community, and are the proposed engagement mechanisms appropriate for the current study?
- What should the direct benefits of the research be for the community involved?
- Does the research question answer a community priority?
- How will the findings be translated into action to address the identified priority area?
- How will possible individual and community harm be minimised?
- Will the research conduct a stakeholder analysis, or are there independent sources available from which the relevant information can be obtained?
- Will the research establish a CAB, or is there a CAB already present in the area? If one still needs to be established, what process has to be undergone for establishing the CAB, and will the anticipated process be both inclusive and democratic?
- How will the study explore the power dynamics among the different community stakeholders to ensure the true representation of the wider community?
- Are the responsibilities of researchers towards the participants, the wider community and the CAB clearly defined?
- How will community consultation and partnership building be sustained throughout the research project’s life cycle?
- Will the researchers concerned be guided by a communications plan in terms of the process and the end-of-study results dissemination?
- Has the committee taken note of project documents related to community engagement that have yet to be developed in full and presented to the committee for ethical approval? (Such documents could include: the communications plan; the community engagement plan; the related standard operating procedures (SOPs); and the information, education and communications (IEC) materials pertaining to the study.
- Will the research project recruit staff from local or central government health institutions, and, if so, will this compromise or weaken the community health system involved?
RECs can promote community engagement in the research process by employing different strategies. First, RECs should include members with experience in community-engaged research and/or members who understand the context and the cultures of the communities in which the research is conducted. Second, at least one REC member must represent the community from which the participants are usually recruited, and must be trained in research ethics to assist them in the REC decision-making process.

THE ROLE OF COMMUNITY MEMBERS IN THE REC

According to Collins et al, the role of community members in the REC should be the following:
- to evaluate the benefits and risks to the research participants concerned;
- to review the informed consent process, in order to ensure the protection of participants;
- to review the protocols involved;
- to help to ensure that language and other aspects of a study make sense to the layperson, and
- to make presentations to community groups regarding the role of RECs, and the importance of human subject research. (29)

Community engagement is a critical factor with regard to the successful translation of research findings into action. RECs must ensure that a community research results dissemination plan is included in the REC research application, and that it makes provision for specifically approving or requesting changes to the plan.

The process of developing equitable working partnerships with organisations that are external to the research institution might raise ethical questions that the REC has not previously considered. The REC should understand the communities’ values and priorities when conducting activities collaboratively with different community organisations. Such engagement should go some way towards dispelling any sense of distrust that might otherwise have been present, and it should also expand the reach of prevention and treatment advances into the communities concerned.

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Health researchers may be confronted with the need, sometimes dire and/or urgent, of participants for additional health care that does not form part of the research objective. Belsky and Richardson define ancillary care as health care required by participants, which is not necessary for the validity of the scientific design, for the safety of the participant, nor for redressing a participant’s injury. (1, 2) The health care needed is therefore unrelated to the research aim(s). A good example is the detection of tuberculosis in a patient, who is participating in a clinical drug trial for new HIV drugs. These ancillary care obligations are positive duties and are not limited to the disease that is the aim or focus of the research. (2)

The question at the heart of the ancillary care debate is to what extent the researcher, and/or other research stakeholders such as sponsors, should be responsible for the treatment of a participant’s health care needs that are not part of the study objective, but for which the participant may expect care? This question is of particular concern when the research is conducted in low- and middle-income countries (LMICs), where access to medical care may be variable and limited. (3) Following the historical trend, in which researchers referred participants to local public health care facilities for ancillary health care needs, makes sense in principle, because this reflects shared responsibility, particularly if researchers plan to build sustainable capacity in local facilities. However, in some communities participants will have limited, and variable, access to even basic health care through government services. (4) When health care services are unreliable,
ancillary care duties are arguably as much in question as when health care services do not exist.

Various proponents have argued both against, (5) and for, (1, 2, 6, 7, 8) ancillary care duties. Arguments in favour of ancillary care responsibilities are based on varied justification. Some motivate for the duty to provide this care in the name of justice, either as a means to reducing inequalities in health care between collaborating nations, (6) as a fair balance of research-related risks and benefits, (7) or as an act of reciprocity. (8) Others claim the grounds for this duty is beneficence. (1, 2) The beneficence argument rests on the notion that if a stakeholder can provide benefit, e.g. ensuring, providing or facilitating access to ancillary health care, without sacrificing anything of comparable significance, they ought to do it. This has also been referred to as the ‘Good Samaritan’ argument. (9) Richardson and Belsky (1, 2) support this beneficence argument and propose that researchers owe their participants more than merely what the research protocol may stipulate. They argue that prospective participants trust researchers to be knowledgeable and in possession of the ability to ensure access to health care, when they give consent to researchers for medical information and research procedures. (1,2) This trust is based on the underlying relationship between the researcher and participant and the need for ancillary care influenced by the vulnerability of the individual participant.

All researcher-physicians are bound by the dictum in the Helsinki Declaration, which declares, “the health of my patient will be my first consideration”. (10) In reality, however, it may be very difficult for researchers to provide all the ancillary health care needs of research participants in these resource-scarce medical environments, especially since research budgets are limited. (3) Barsdorf et al reported that potential research participants are not expecting sponsors of vaccine trials to bear the sole burden of providing health care, but they do expect that researchers should assist participants in accessing care, since: 1. they are able to do so; and 2. they have a relationship with participants. (11) This resonates with the beneficence argument. It also counters the fear of unrealistic and inappropriate costs crippling research, an argument against ancillary care obligations that has been present in this debate. (5, 12)

There are currently no extensive guidelines to assist the researcher-physician and the topic is still strongly debated between researchers, academics and ethicists. The Commentary to the Council for International Organisations of Medical Sciences’ guidelines and the Nuffield guideline suggest that, based on constructive dialogue between sponsors, researchers, local health care providers and the research community, a comprehensive care package should be negotiated prior to the start of the research process. (13, 14) It is very important that the expectations of the communities involved, are taken into consideration, to ensure public trust. (13, 14) Weijer and LeBlanc suggest that this “moral negotiation” will ensure that communities have the opportunity to determine potential benefit that will address their health care priorities. In addition, this process of community engagement upholds the principle of respect for persons. (15)
The HIV Prevention Trials Network (HPTN) is an example of a sponsor who led the way and engaged seriously with their ancillary care responsibilities, implementing these in both policy and practice. The researchers at trial sites negotiated buy-in from local government, and other partners, to jointly fund and facilitate accessible provision of ancillary care. (16) Their example exemplifies the concept of “moral negotiation” in the research process where researchers and sponsors negotiate with increasingly empowered local communities and host countries to achieve meaningful and substantive benefits from biomedical research. (15)

Research Ethics Committees (RECs) need to ask the following questions when reviewing a research protocol with the possibility of ancillary care obligations (3):

1. What are the potential needs for ancillary-care during the research process? Have researchers determined the disease burden of the community where the research is conducted, as well as what co-morbidities may be revealed during the research process, necessitating medical care?
2. Will the local health system be able to address these health care needs and do the necessary health care facilities exist? Can the existing health care system cope with the workload and are the necessary medical staff and other health care personnel available?
3. What will be the responsibility of both the researchers and the sponsors in terms of this ancillary care obligation? Towards determining this: What is the severity of the co-morbid disease, and the consequences if not treated? Are the ancillary care needs incidental to the research process or an integral part of the study procedures? What are the potential costs, staff time and influence on the study goals? Has the researcher defined the role of both the researchers and the sponsors in the provision of ancillary care?

Richardson et al propose four guidance points regarding ancillary care (“The Four P’s”) are as follows (3):

1. **Positive duty:** Both researchers and sponsors have a moral obligation to address the ancillary care needs of research participants. This is especially important for research conducted in LMICs with limited resources.
2. **Planning:** In determining the burden of disease in the target community prior to the research process, the researchers will be able to plan for the potential ancillary care needs, taking cognizance that unexpected ancillary care needs may arise. Researchers should develop action plans for these ancillary care needs.
3. **Partnership:** The researchers should enter into a dialogue with both the target community and the local health care system to develop prospective plans to address these ancillary care needs. These plans should incorporate the local health care structures.
4. **Practical provisions:** Both researchers and sponsors should meet their ancillary care obligations by taking practical steps to address them. This may include provision in the budget for funding some of the ancillary care, creating a partnership with the local health authorities or hiring a physician for the ancillary care needs.
This chapter offers some guidelines to REC members reviewing research with potential ancillary-care responsibilities. We need further empirical and conceptual research on ancillary care in Africa to further define guidelines for the continent.

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PART IV

RESOURCES
INTRODUCTION

External government agencies and charitable foundations fund the majority of clinical research conducted in Africa. These include the National Institutes of Health (NIH) of the USA, the EDCTP, Welcome Trust and the Bill and Melinda Gates Foundation, to name but a few. This funding has allowed much needed research in Africa, particularly into previously neglected diseases such as tuberculosis, malaria, trypanosomiasis and many others. However, such funding often comes with many regulatory compliance constraints that RECs must be aware of. Failure to recognise and comply with these requirements can result in a range of consequences from the suspension of research activities to cancellation of studies and repayment of funds. It is beyond the scope of this short overview to provide detailed information. The necessary information is always available on relevant websites and subject to change. Thus the purpose of this section is simply to alert RECs to this very important issue and provide some basic information. What is of utmost importance is that RECs also ensure that while complying with regulations and ethical standards set by international funding agencies, they also comply with the national regulatory framework of their own country. For example, many African countries including South Africa now also have a legal framework for health research that involves human participants. These legal requirements must also be upheld. Where conflict arises the REC must always decide to implement the stricter requirement.
This chapter focuses on procedural issues and does not specifically address the ethical issue associated with the dual review of research by local and western or northern collaborating partner RECs. It is, however, important that RECs take cognisance of the mandate, functions and SOPs of other RECs also involved in reviewing the same research protocols and those differences of opinion are addressed through direct communication between RECs, rather than through the investigators.

RESEARCH FUNDED BY US FEDERAL AGENCIES

Such agencies include the NIH and all its institutes and USAID. All institutions conducting research involving human participants that are funded by US federal (government) funding must agree to comply with all relevant US research-related documentation. This agreement comes in the form of a signed assurance called a Federal Wide Assurance (FWA)\(^1\). The paperwork or form can be downloaded from the website of the US Office for Human Research Protections (OHRP)\(^2\) and must be signed by the head of the institution concerned, for example the Provost: Research or the director of the research centre or institution, as the case may be. The signed documentation must then be submitted electronically to the OHRP for approval. The institution will then be given a FWA number and be registered on an international database. The institutions FWA lasts for three years and must be renewed before it expires.

As part of the FWA process the institution will have to nominate a REC (Institutional Review Board or IRB as per the US nomenclature) that is registered with the OHRP. The REC/IRB usually is part of the research institution (for example a university). However, some research institutions may be small and not have their own REC/IRB. They can then, with the agreement of another local institution, nominate that institution’s IRB. Obviously the other (external) institution must be prepared to agree to this and their institution must have OHRP registration. In countries with national RECs, the institution may nominate the national REC if it is registered with the OHRP. Details about this process can be obtained from the OHRP website.

African institutions receiving US federal research funds will also be required to sign an assurance with the Office for Research Integrity.\(^3\) Once a year the institutional official (the person who represents the institution and signed the assurance) will be requested to confirm, via an electronic process, that there have been no alleged cases of research misconduct at the institution in the previous year and that there are no cases under investigation. Research misconduct includes plagiarism, data falsification

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\(^1\) Additional information can be found at http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html [Accessed 1 November 2013]


\(^3\) Office for Research Integrity (USA) https://ori.hhs.gov/ [Accessed 1 November 2013]
or data fabrication). It is also a requirement that all drug trials funded by US Federal Agencies are registered with a publicly available database (www.clinicaltrials.gov) before recruitment of the first patient/participant.

Finally, all health research studies involving human participants must comply with the regulation for research described in the United States Code of Federal Regulations Title 45 Part 46. These regulations can be downloaded at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html In particular there are very specific REC/IRB requirements for the review of research involving children, pregnant women and prisoners that must be strictly adhered to over and above the general review requirements described in this legislation. It is essential that African RECs reviewing US-funded research are familiar with the requirements stipulated in these regulations and adhere to them and ensure that the researchers involved do likewise. For example, there are specific requirements for the annual continuing review of research that if not complied with can lead to suspension of the project. See http://www.hhs.gov/ohrp/policy/continuingreview2010.html

EUROPEAN UNION FUNDED RESEARCH

Researchers conducting research funded by an agency or programme falling under the auspices of the EU must be sure to familiarise themselves with funding requirements for ethics review and compliance. Generally EU requirements are less bureaucratic than US requirements but should nevertheless be closely adhered to. In particular clinical trials funded by any EU countries, agencies or companies that may lead to registration and marketing of new drugs will most likely need to adhere to the EU Clinical Trials Directive 2001/20/EC. More information can be found at http://ec.europa.eu/health/human-use/clinical-trials/

CHARITABLE FOUNDATION FUNDED RESEARCH

There are now many charitable foundations funding health research initiatives, particularly in the developing world. Each foundation has their own set of requirements regarding ethics approval of research and reporting of progress and findings. REC should ensure that researchers are aware of these requirements and that they comply with them. RECs must also ensure that they are aware of any specific requirements that may pertain to the review of any particular project. For example, an REC that usually makes decisions by way of a consensus agreement may be required to report on the actual voting statistics for a particular project. (This is also a requirement for NIH funded projects.)

In conclusion, it is the responsibility of both RECs and researchers to ensure that they are aware of and up-to-date with the complex requirements of both funders and regulatory agencies with respect to the ethics review and approval of research projects involving human participants.
INTRODUCTION

Educational resources in research ethics can be broadly divided into self-education opportunities or formal training programmes. The latter are offered by many different institutions and organisations, and at several levels, leading, in most cases, to the awarding of either a certificate or a diploma. This chapter deals primarily with the various training programmes available. A list of useful reading resources is also provided. Importantly, the information provided in this chapter was up-to-date and validated just prior to publication. However, it is liable to change at short notice, with new programmes becoming available and other programmes being withdrawn. The reader is advised to check information by using the links provided or perform their own internet searches.

For ease of reference, the training will be divided into the following:

1. Online courses
2. Short certificate and diploma courses
3. Master’s and doctoral programmes

The target audience may vary, but includes research ethics committee (REC) members, clinicians, other health care professionals, researchers, community advisory board (CAB) members, lay members, and ethicists. Several training programmes are funded through various mechanisms in order to build capacity. In-depth education includes master’s and PhD programmes, of which some offer scholarships, which are limited to those in countries of target or specific groups. Table 1 provides a summary of NIH Fogarty-funded programmes in research ethics (see below).
ONLINE COURSES

The international ethics courses that are currently available online are accessible to a broad audience. The courses concerned are listed alphabetically.

Collaborative Institutional Training Initiative (CITI) Program
(https://www.citiprogram.org/default.asp?language=english)

The CITI Program was established in 2000 as a web-based training platform between the University of Miami and the Fred Hutchinson Cancer Research Center. The programme offers research ethics education opportunities to all members of a research team. Students should be affiliated with a CITI-participating institution or organisation, of which there are more than 1500 worldwide. The education content can be adapted to an individual institution’s needs. On completion, the student can print out a certificate as proof of learning.

Family Health International 360 programme

Family Health International (FHI) 360 offers an online ethics course that is available in English, Spanish, Portuguese and French. Currently, the second edition of the course is available, which can be read offline as a self-study programme. The content covers: the principles of research ethics; the development of contemporary research ethics; informed consent; responsibilities of research ethics committees; responsibilities of sponsors and researchers, and community participation in the research process. The course uses case studies, assessment, and additional resources. Upon successful completion with an average of 80% or more, the student can print out a certificate.

Global Health Reviewers
(http://globalhealthreviewers.tghn.org/elearning/)

Global Health Reviewers offers more than 80 online courses in research ethics. Of particular interest is a free online training course on genomic research, due to the ethical issues related to the review of genome-wide association studies (GWAS) protocols that are rapidly increasing in number. (http://globalhealthtrials.tghn.org/elearning/education/lectures/elearning-courses/introduction-to-reviewing-genomic-research/)

National Institute of Health program
(http://phrp.nihtraining.com/users/login.php)

The National Institute of Health (NIH) office of Extramural Research offers a course on Protecting Human Research Participants (PHRP) that is downloadable upon
registration, and which takes approximately three hours to complete. A certificate is issued after completion of the seven modules and the four quizzes, upon achieving a satisfactory score.

Public Responsibility in Medicine and Research
(http://www.primr.org/ Conferences.aspx?id=8523)
Public Responsibility in Medicine and Research (PRIM&R) has launched a new online training course for IRB members, which is entitled ‘Ethical Oversight of Human Subject Research’. Access to said four-hour course requires the payment of annual fees at an individual (PRIM&R member/non-member), or institutional, level.

The Center for Bioethics, College of Medicine, University of Ibadan
(http://bioethicscenter.net/web/index.php/about-wab/wab-programs/ ) (Table 1)
The Center for Bioethics offers an annual online diploma course that focuses on the foundations of modern bioethics and informed consent. The programme is sponsored by Fogarty International Center. The above-mentioned CITI certificate is required to apply for the diploma course.

Training and Resources in Research Ethics Evaluation
(http://elearning.trree.org/)
Training and Resources in Research Ethics Evaluation (TRREE) is an EDCTP-funded initiative, which was first launched in 2009. The target audience includes REC members, researchers, and other health care professionals. The four modules are: (1) Introduction to research and research ethics; (2) Research ethics evaluation; (3) A country-specific module for certain countries, which is currently available for Burkina Faso, Cameroon, Ivory Coast, Mali, Mozambique, Nigeria, Senegal, South Africa, and Tanzania, and (4) specific issues, including informed consent. The training is available in English, French, and Portuguese. Students should achieve 60% on completion in order to obtain the TRREE Certificate.

University of Maryland initiative
(http://menareti.net/new/) (Table 1)
The Global Ethics Educative Initiative (GEEI) at the University of Maryland offers an online training in Research Ethics, on successful completion of which a certificate may be printed. MERETI is also a Fogarty funded training programme.
SHORT CERTIFICATE AND DIPLOMA COURSES

The training programmes in this section are intensive short courses, which usually last over a week. The target participants are researchers and REC and CAB members, and the courses are ranked in alphabetical order.

Advancing Research Ethics Training in Southern Africa
(http://sun025.sun.ac.za/portal/page/portal/Health_Sciences/English/Centres%20and%20Institutions/Bioethics1/ARESA/)

The Advancing Research Ethics Training in Southern Africa (ARESA) is a Fogarty-funded collaborative research ethics training programme that is jointly run by the Centre for Medical Ethics and Law, Stellenbosch University and the Center for Bioethics, University of North Carolina, Chapel Hill, USA. The programme offers a postgraduate Diploma in Health Research Ethics (HRE) to mid-career professionals, including experienced researchers, clinicians and REC members who are resident in South Africa, or in neighbouring African countries. The diploma programme consists of three modules of two weeks each that are held over the course of one year.

Center for Bioethics, College of Medicine, University of Ibadan
(http://bioethicscenter.net/web/index.php/education/online-diploma-courses) (Table 1)

The Center for Bioethics in Ibadan, Nigeria offers an annual online Diploma Course in Informed Consent and Foundations of Modern Bioethics. The programme, which is funded by the NIH-FIC and the National Human Genome Research Institute, is open to West African individuals who wish to learn more about research ethics and bioethics, but who are not available to register for the Master’s Bioethics Programme at the University of Ibadan (see Section 3 below). The duration of the course is two months.

Council on Health Research for Development

The Council on Health Research for Development (COHRED) and the Global Fund, by way of a grant to the Global Forum on Health Research, funded the first African Conference for Administrators of RECs (AAREC), which was held in Kasane (Botswana) in September 2011 (http://www.healthresearchweb.org/files/AARECFinalReport.pdf). The first-ever association of African REC administrators was launched during this meeting (Evelyn Anane-Sarpong, personal communication). Other AAREC meetings might follow in future.

Indiana University
(www.nationalethicscenter.org)

The Training Research Ethics (TRE) programme at Indiana University, Bloomington, Indiana, offers training to trainers in research ethics on an annual basis.
Educational Resources for Research Ethics

Johns Hopkins Berman Institute of Bioethics
(http://www.bioethicsinstitute.org/web/page/1044/sectionid/378/pagelevel/2/interior.asp)
The Johns Hopkins Berman Institute of Bioethics, Baltimore, Maryland offers summer courses in bioethics through the Berman Institute Bioethics Intensives (BI²) programme. The week-long intensive courses in bioethics target students, medical/legal/policy professionals, researchers, and scholars.

Johns Hopkins Bloomberg School of Public Health
(http://www.jhsphealth.edu/courses/course/340.667/11/2012/15691/)
The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland offers a one-week intensive summer course entitled 'Ethics Issues in Human Subjects Research in Developing Countries'. The course is offered as part of the Johns Hopkins Graduate Summer Institute of Epidemiology and Biostatistics. Course enrolment is open to any interested practitioner, researcher, funder, faculty member, or student.

The Johns Hopkins–Fogarty African Bioethics Training Program
(http://www.fabtp.com/) (Table 1)
The Johns Hopkins–Fogarty African Bioethics Training Program (FABTP) is a capacity development partnership in research ethics that targets African institutions. Scholars spend six months at the Johns Hopkins Bloomberg School of Public Health and Bioethics Institute, attending courses and seminars. The last six months is spend in their home countries, where they conduct a research project into research ethics issues in their home country under the mentorship of their teachers.

The Kennedy Institute of Ethics
(http://kennedyinstitute.georgetown.edu/programs/ibc.cfm)
The Kennedy Institute of Ethics in Georgetown University, Washington DC, annually offers a one-week Intensive Bioethics Course (IBC) that is designed for health care practitioners, policy-makers and clinical researchers.

Steve Biko Centre for Bioethics
(http://www.wits.ac.za/academic/health/centres/18236/short_courses.html)
The Steve Biko Centre for Bioethics at the University of the Witwatersrand Faculty of Health Sciences in Johannesburg, South Africa offers a short course in ‘Research Ethics: Conducting Research Responsibility’, in the form of a three-to-five-day training workshop, targeting REC members, research regulators, and researchers who have not previously been exposed to research ethics training, and who reside in Africa. This initiative has been supported by an educational grant from Pfizer. A certificate of competence is awarded to participants upon successful completion of the evaluation.
Centre for Biomedical Ethics and Culture, Sindh Institute of Urology and Transplantation, Karachi
(http://www.siut.org/bioethics/index.html)

The Centre for Biomedical Ethics and Culture offers a postgraduate diploma. The target is mainly Pakistani citizens, although foreign students may be admitted. The training provides a scholarship for tuition and living expenses, but students have to pay for the costs of their travel to the training. The training is modular and requires attendance at four face-to-face, Karachi-based didactic sessions that are spread over a period of 18 months.

MASTER’S AND DOCTORAL PROGRAMMES

The master’s programmes offer in-depth research ethics training, and require attendance over a period of either 12 or 24 months. The programmes concerned are listed alphabetically below:

The Bioethics Unit, Aga Khan University
(http://www.aku.edu/collegesschoolsandinstitutes/medicine/pakistan/programmes/graduate/masterinbioethics/Pages/masterinbioethics.aspx) (Table 1)

Since 2008, the Bioethics Unit of Aga Khan University has offered an NIH-FIC funded master’s degree in bioethics that takes place over 24 months, and which consists of seven modules. The aim is to develop expertise in bioethics in Pakistan and in resource-poor countries that are located in the Eastern Mediterranean region. Eligible countries in Africa include Djibouti, Egypt, Somalia, Sudan, and Tunisia.

The Center for Bioethics, College of Medicine, University of Ibadan
(http://www.bioethicscenter.net/postgraduate/) (Table 1)

Since 2007, the University of Ibadan has offered a FIC-funded master’s degree in bioethics as part of the West African Bioethics (WAB) training programme. The degree, which consists of a modular-based programme, requires the successful completion of a research project dissertation. The entire curriculum can be completed within three consecutive semesters.

The Indiana University Center for Bioethics
(http://bioethics.iu.edu/programs/arep/) (Table 1)

The Indiana University (US) has developed a long-standing partnership in East Africa with the Moi University School of Medicine in Western Kenya. The Indiana University–Moi University Academic Research Ethics Partnership is funded by the NIH-FIC to provide training in the form of a master’s in International Health Research Ethics
(MIHRE). The programme comprises coursework, examinations, and a practicum, or research thesis, which all must be completed in a period of between two and four years.

The Joint Centre for Bioethics, University of Toronto
(http://www.jointcentreforbioethics.ca/education/mhsc.shtml) (Table 1)

The University of Toronto Joint Centre for Bioethics offers a postgraduate degree programme in bioethics. The professional Master’s of Health Science in Bioethics is a full-time programme that is offered in 24 two-day blocks from September to April over the space of two years. It is a professional master’s degree programme that does not require a thesis. The Collaborative Program in Bioethics, however, requires that students conduct innovative research in relation to the discipline in their home department.

The South African Research Ethics Training Initiative (SARETI)
(http://sareti.ukzn.ac.za/Education.aspx) (Table 1)

The SARETI programme is an FIC-funded master’s programme in health research ethics that is presented at the University of KwaZulu-Natal. The course, which consists of multidisciplinary modules, requires a dissertation providing proof of original research into research ethics issues. Four scholars from Africa are annually selected, in terms of highly competitive criteria, to participate in the programme, according to their professional expertise, leadership ability, and potential for ethics research.

Of note, the SARETI programme has its counterpart in the Middle East, in the form of the MERETI (Middle East Research Ethics Training Initiative) programme, which is linked to the University of Maryland School of Medicine, and which also targets North African candidates. (http://medschool.umaryland.edu/mereti/)

The Steve Biko Centre for Bioethics
(http://www.wits.ac.za/academic/health/centres/bioethics/10059/academic_programmes.html)

The Steve Biko Centre for Bioethics (which is described above in section 2) offers a master’s programme in bioethics and health law. The programme includes six modules (of which four are compulsory and two elective) that require full-time attendance, and a research dissertation. The target audience is composed of health care practitioners, academics, lawyers, social scientists, and members of RECs from across Africa.
FORUMS AND NEWSLETTERS

□ To the best of our knowledge, there is one major electronic mailing list that contains extensive information on bioethics. The INTERNATIONAL-BIOETHICS-L mailing list (Communication in International Research Ethics) is an initiative of the NIH-FIC. Once or twice a week, announcements of meetings and funding and training opportunities, as well as articles, are forwarded by means of this list. All of the relevant information about the bioethics training programmes, including contact information for the grantees, is on the FIC/NIH website (http://www.fic.nih.gov/programs/training_grants/bioethics/index.htm). All REC members are advised to register for receipt of the list at international-bioethics-l@list.nih.gov.

□ Several institutions disseminate information in the form of newsletters. For example, the WHO publishes the *Ethics and Health Unit Newsletter*, which is available from http://www.who.int/ethics, or, alternatively, via subscribing to the mailing list by way of sending a request to ethics@who.int. The WAB publishes a newsletter that covers details relating to the WAB Training Programme at http://bioethicscenter.net/web/index.php/about-wab/wab-newsletter-publications.

BOOKS

A selection of books that might be of interest to REC members is provided below, assuming that the fundamental texts, such as the Declaration of Helsinki (of the World Medical Association), the International Ethical Guidelines for Biomedical Research involving human subjects (of the Council for International Organisations of Medical Sciences) and the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use are known. Of note, only the title, the year and the weblink are provided, since accessing details of the book via the weblink will give access to all other important publication details. The following books have been ranked in chronological order.


Educational Resources for Research Ethics

- Standards and operational guidance for ethics review of health-related research with human participants (2011) http://www.who.int/

CONFERENCES WITHIN THE FIELD OF ETHICS AND RELATED ASSOCIATIONS

Attending a conference within the field of ethics can be considered as a form of continuous education. A few examples of such conferences are described below.

Public Responsibility in Medicine and Research (http://www.primr.org/)
PRIM&R organises annual Advancing Ethical Research conferences in the US, for which a limited number of international scholarships are available. Of note, priority is given to first-time applicants and to those who submit a poster abstract.

The Global Summit of National Bioethics Advisory Bodies (http://www.who.int/ethics/globalsummit/en/)
All national bioethics advisory bodies are invited to attend the Global Summit of National Bioethics Advisory Bodies, which takes place every other year. The 9th such summit took place in Africa for the first time in 2012 (to be more precise, in Carthage, Tunisia during September). Any government or national commission wishing to attend the next global summit, or to be added to the relevant emailing list, should send a request to ethics@who.int.

World Congress of Bioethics (http://bioethics-international.org/index.php?width=1360&height=768&show=index)
The International Association of Bioethics organises the World Congress of Bioethics every other year. The issue of ethics and research in developing countries was discussed at the 11th Congress that took place in Rotterdam in 2012.
International Association for Education in Ethics International Conference

(http://www.duq.edu/academics/schools/liberal-arts/centers/center-for-healthcare-ethics/international-association-for-education-in-ethics/iaee-international-conference)

The International Association for Education in Ethics (IAEE), which was created in 2011, organised its First International Conference on Education in Ethics in 2012 at Duquesne University, Pittsburgh, Pennsylvania. The Association is housed in the Center for Healthcare Ethics at Duquesne University.

OTHER RESOURCES

This section provides some information on programmes that support capacity-building activities in ethics for African institutions and ethics committees. RECs are encouraged to apply for funding from said initiatives in order to support their own, or else regional, capacity development programmes.

European and Developing Countries Clinical Trials Partnership (EDCTP)


The EDCTP has played a key role in awarding ethics grants to institutions in sub-Saharan countries that have allowed national ethics committees, research ethics committees, ministries of health and universities to strengthen their research ethics capacities among African scientists, and their capacities in ethical review among African REC members.

Fogarty’s International Research Ethics Education and Curriculum Development Award

(http://www.fic.nih.gov/programs/pages/bioethics.aspx)

Fogarty’s International Research Ethics Education and Curriculum Development Award has been designed to encourage the development of culturally relevant bioethics curricula for developing scientists of national note, and to support training that is aimed at producing leaders who could advise on policy, and help to train the next generation.
Table 1: NIH Fogarty-funded programmes established by trained African scholars after 2000 (also listed above under appropriate sections)

<table>
<thead>
<tr>
<th>Programme</th>
<th>Acronym</th>
<th>Period of operation</th>
<th>Host Institutions</th>
<th>Countries/Regions of focus</th>
<th>Level of training offered</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Research Ethics Training Programme</td>
<td>IRETP</td>
<td>2000-2016</td>
<td>Case Western Reserve University</td>
<td>Nigeria and Uganda</td>
<td>Master’s</td>
</tr>
<tr>
<td>University of Toronto MHSc in Bioethics International Stream</td>
<td>UTMBIS</td>
<td>2000-2012</td>
<td>University of Toronto</td>
<td>West Africa</td>
<td>Master’s</td>
</tr>
<tr>
<td>International Research Ethics Network for Southern Africa</td>
<td>IRENSA</td>
<td>2002-2012</td>
<td>University of Cape Town</td>
<td>Southern Africa</td>
<td>Diploma</td>
</tr>
<tr>
<td>South African Ethics Training Initiative (SARETI)</td>
<td>SARETI</td>
<td>2002-2016</td>
<td>University of KwaZulu-Natal</td>
<td>Sub-Saharan Africa</td>
<td>Certificate &amp; master’s</td>
</tr>
<tr>
<td>Middle Eastern Research Ethics Training Initiative</td>
<td>MERETI</td>
<td>2004-2016</td>
<td>University of Maryland</td>
<td>North Africa + Sudan</td>
<td>Certificate</td>
</tr>
<tr>
<td>West African Bioethics Training Programme</td>
<td>WABTP</td>
<td>2004-2016</td>
<td>University of Maryland, University of Ibadan</td>
<td>West Africa</td>
<td>Master’s &amp; certificate</td>
</tr>
<tr>
<td>Strengthening Bioethics Capacity and Justice in Health</td>
<td>SBCJH</td>
<td>2004-2012</td>
<td>University of North Carolina at Chapel Hill</td>
<td>Democratic Republic of the Congo, Madagascar</td>
<td>Masters &amp; PhD</td>
</tr>
<tr>
<td>Training for Scholarships in Research Ethics</td>
<td>TSRE</td>
<td>2004-2008</td>
<td>Michigan State University, University of Malawi</td>
<td>Eastern and Southern Africa</td>
<td>Master’s &amp; certificate</td>
</tr>
<tr>
<td>Indiana University–Moi University Academic Research Ethics Partnership</td>
<td>IU–Moi AREP</td>
<td>2008-2012</td>
<td>Indiana University, Moi University</td>
<td>Kenya</td>
<td>Master’s</td>
</tr>
<tr>
<td>Dartmouth/Penn Research Ethics Training and Program Development for Tanzania</td>
<td>DPRET</td>
<td>2011-2016</td>
<td>Dartmouth College</td>
<td>Tanzania</td>
<td>Master’s</td>
</tr>
<tr>
<td>Advanced Research Ethics Training for Southern Africa</td>
<td>ARESA</td>
<td>2011-2016</td>
<td>Stellenbosch University</td>
<td>Southern Africa</td>
<td>Diploma</td>
</tr>
</tbody>
</table>
CONCLUSION

This chapter enumerated a number of educational opportunities that are available for REC members, ranging from online and short courses to degree programmes. Although an attempt has been made to compile a comprehensive guide to research ethics learning opportunities, the list, as it is given here, may be unfinished and subject to fluctuations across time. On the one hand, some programmes may have a limited lifetime, due to their having been initiated through specific external grants. On the other hand, the field of ethics, and especially of research ethics, is witnessing increasing interest worldwide; therefore, new initiatives and opportunities are likely to emerge daily.
A Self-Assessment Tool to Assess Operational Characteristics of Research Ethics Committees in Developing Countries

Henry Silverman, Hany Sleem

Key Message: This chapter shares with RECs in the developing world an accessible self-assessment tool, based on international standards, that incorporated metrics considered foundational for effectiveness of REC.

INTRODUCTION

Research involving human participants, especially clinical trials, has increased in the developing world. (1) In response, research ethics committees (RECs) have been established in universities, research institutions, non-governmental organisations, and ministries of health. However, the functioning of these RECs remains unknown. Several studies have shown that RECs face challenges that prevent their optimal functioning. (2-8) Accordingly, commentators have expressed concerns with the functioning of RECs in the developing world and their capability to perform adequate and consistent ethical reviews. (9, 10) As such, there has been a growing interest in establishing mechanisms to assess the operations and functions of RECs.

Recently, there have been initiatives to formally evaluate RECs via an accreditation process that represents an external review mechanism based on standards drawn from current regulatory requirements. Examples of such accreditation efforts include the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) (11) and the Association for the Accreditation of Human Research Protection Programs (AAHRPP), a private organisation based in the US. In the United Kingdom, the National Research
Ethics Service has developed an accreditation process that includes IRB registration, self-assessment, and regular audits of the IRBs. (12) In South Africa, the National Health Research Ethics Council (NHREC) conducted its first audit of all 33 registered RECs in 2012. (13)

Since few resource-limited countries have a legal or regulatory framework for clinical research, an accreditation process consisting of an external review mechanism based on national standards is problematic for many countries in the developing world. Instead, a method of self-assessment might prove to be an intermediary step to help RECs evaluate their performances and demonstrate to their stakeholders the legitimacy of their review mechanisms.

As such, we developed an accessible self-assessment tool for RECs in the developing world based on international standards that incorporated metrics considered foundational for effectiveness of RECs. (14)

This tool contains the following domains: Organisational aspects; policies and procedures of the REC; membership composition and training; submission processes and documents received; recording of minutes, policies and procedures for review, criteria for ethical review; criteria for informed consent; elements of the decision letter: criteria for continuing review, and REC resources. Each question within the domains was assigned a point value: 1, 2, or 5 points; maximum score is 200 points.

To assess the feasibility of this self-assessment tool, REC chairs from three different regions from the developing world (Egypt, South Africa, and India) completed the self-assessment tool. (15) The aggregate mean score for 64 REC was 137,4±35,8; the median score was 145. More than 85% of the RECs thought that the survey will produce useful information and more than 85% completed the survey in less than one hour.

While it is difficult to interpret the meaning of such an aggregate score precisely, one can say that RECs have considerable room for improvement. Also, there are several ways in which a self-assessment tool can provide helpful information to RECs. First, it can serve as a quality improvement mechanism for RECs by identifying which standards are in need for improvement. Second, RECs can use the mean score obtained in our study as a benchmark for how well they are operating in comparison to other RECs in the developing world. Accordingly, chairs can use such data to lobby their top officials for more human and capital resources. Finally, the process of self-assessment can raise awareness regarding the strengths and challenges at the individual REC level.
RESEARCH ETHICS COMMITTEE (REC)
SELF-ASSESSMENT TOOL

The maximum total number of points 200

For ‘yes/no’ questions, points are given for a ‘yes’ response

ORGANISATIONAL ASPECTS (maximum 54 POINTS)

What year was the REC established? ____

1. Is the REC subject to registration with a national authority? Yes ☐ No ☐ 2 points

2. How often does the REC meet as a full committee to review research studies?
   _____ once/week  _____ twice/month  _____ once/month
   _____ every two months  _____ other  _____ has not yet met to review protocol

   For meeting frequency equal or greater than once/month (1 point)

3. Was the REC established under a high ranking authority of the institution (e.g., President’s office, Dean, etc.). Yes ☐ No ☐ 5 points

4. Does the REC have written Standard Operating Procedures? Yes ☐ No ☐ 5 points

5. Does the REC have a policy that outlines the process for appointing the REC Chair? Yes ☐ No ☐ 2 points

6. Which of the following criteria are used to select the Chair of the REC (check all that apply)?
   _____ prior training in ethics  1 point  _____ prior research experience  1 point
   _____ publication in ethics  1 point  _____ other (please describe)

7. Does the REC have a policy that describes the process for appointing the members of the REC and details the membership requirements and the terms of appointment? Yes ☐ No ☐ 2 points

8. Which of the following criteria are used to select REC members (check all that apply)?
   _____ prior training in ethics  1 point  _____ prior research experience  1 point
   _____ publication in ethics  1 point  _____ other (please describe)

9. Does the REC have a policy for disclosure and management of potential conflicts of interest for the members of the REC? Yes ☐ No ☐ 5 points

10. Does the REC have a policy for disclosure and management of potential conflicts of interest for members of the research team? Yes ☐ No ☐ 5 points
11. Does the REC have a quality improvement (QI) programme for itself? 
   Yes ☐ No ☐ 5 points
   If yes, describe what was done in the last year and any changes made as a result of the QI programme.

12. Does the institution/organisation regularly evaluate the operations of the REC (e.g., budget, adequacy of human and material resources, adequacy of policies and procedures and practices, and appropriateness of the membership given the research being reviewed)?
   Yes ☐ No ☐ 5 points

13. Does the REC have a mechanism whereby enrolled research participants can file complaints or direct questions regarding human subjects protection issues?
   Yes ☐ No ☐ 5 points
   If yes, please describe the mechanism

14. How are records of the REC stored? (1 point maximum)
   _____ Paper folders in a locked file cabinet 1 point
   _____ Electronic in a password-protected computer 1 point
   _____ On an open shelf
   _____ Other

15. Quorum: Does the REC require that there be a certain number of members present in order to make the meeting official to review protocols?
   Yes ☐ No ☐ 5 points

Membership and educational training (Maximum 30 points)

1. How many members are there on the REC?
   If > 5 members, 2 points

2. How many are women? _____ How many are men? _____

   If female/total membership ratio is between 0.4 and 0.6, then 2 points

3. Is there a requirement that a top official of the institution (e.g., President, Dean, etc.) who oversees the operations of the REC cannot serve as the chair or member of the REC?
   Yes ☐ No ☐ 2 points

4. Are any of the members not affiliated with the institution, that is, the member is not employed by the institution and is not related to a person who is employed?
   Yes ☐ No ☐ 2 points

5. Are any of the members considered to be a non-scientist?
   Yes ☐ No ☐ 1 point
   A non-scientific member is any member who does not have a terminal degree in a medical or scientific field. Please note, that one member may fulfil both criteria of non-scientist and non-affiliated, in which case, please check Yes for both #3 and #4.

6. Is there a requirement that the REC chair (or the designee that is in charge of running the committee) has any prior formal training in research ethics?
   Yes ☐ No ☐ 5 points

7. Does the institution require that REC members have training in research ethics inorder to be a member of the REC?
   Yes ☐ No ☐ 5 points
8. Does the institution require that investigators have training in research ethics in order to submit protocols for review by the REC? Yes □ No □ 5 points

9. Does the REC conduct continuing education in research ethics for its members on a regular basis? Yes □ No □ 5 points

10. Does the REC document the human subjects protection training received by its members? Yes □ No □ 1 point

Submission arrangements and materials (Maximum 12 points)

**Submission arrangements of research protocols** (1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC publish guidelines for submission of applications for the review by the REC?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC require investigators to use a specific application form for their submission of their protocols to the REC?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC have an informed consent template to help guide investigators in the writing of their informed consent forms?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC require approval and signature of the department chair (or another individual) of the research protocol prior to the submission?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC require a deadline for investigators to submit protocols for full committee review?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Submission Materials** (1 point each)

Which of the following items are requested from the Principal Investigators when they submit their research protocol to the REC?

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator’s qualifications (e.g., CV, medical licence(s), etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conflict of interests disclosure forms for members of the research team</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment material (e.g. advertisements, signs, posters, etc.), if applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires/surveys that will be used in the research, if applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigators’ drug brochure or materials describing the nature of the drug being used in a clinical trial, if applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Minutes

Does the REC maintain minutes of each meeting?  

Yes ☐  No ☐  5 points

If minutes are kept, please answer the following questions regarding the minutes  

(1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do the minutes reflect that members were asked whether they had a conflict of interest regarding any of the protocols to be discussed and indicate that such members did not participate in the decision making process of the relevant protocols?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes document that a quorum was present for all actions requiring a decision?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes document that all actions included at least one scientist in the review and participated in the decision making process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes document that all actions included at least one non-scientist in the review and participated in the decision making process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes document that all actions included at least one person who is not affiliated with the institution in the review and participated in the decision making process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes record the name of REC members who abstained from the decision making process and provided the reason for abstention?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes record the name of REC members who were excused from the discussion and decision making process due to a conflict of interest?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the minutes reflect, when applicable, a discussion of the controversial aspects of the research protocol?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Policies referring to review procedures

(1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC have a policy on protocols review?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC bring in a consultant when necessary to provide scientific or other relevant expertise for review of a particular protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do REC members receive the protocol and other materials at a specified time prior to the meeting?</td>
<td></td>
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<tr>
<td>Does the REC require reviewers to use a checklist to document their ethical assessment of the research submission?</td>
<td></td>
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<tr>
<td>Does the REC have a policy on the conditions for expedited REC review?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC have a policy on the conditions for qualifying for exempt status of studies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC determine the interval of continuing review based on the risk of the study?</td>
<td></td>
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<tr>
<td>Does the REC have a policy for how decisions are made (e.g. consensus or a vote)?</td>
<td></td>
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</tr>
<tr>
<td>Are members asked at the beginning of the meeting if they had a conflict of interest in respect of any of the protocols to be discussed, and is it indicated that such members did not participate in the decision on the relevant protocols?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC have a policy for communicating a decision?</td>
<td></td>
<td></td>
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<tr>
<td>Does the REC have a policy for follow-up review?</td>
<td></td>
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</tr>
</tbody>
</table>
### Review of specific protocol items

#### Scientific Design and Conduct of the Study

(Maximum 43 points)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC review the suitability of the investigators’ qualifications to conduct the study?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC review the adequacy of the clinical site, including the supporting staff, available facilities, and emergency procedures?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC take into account prior scientific reviews or do they review the appropriateness of the study design in relation to the objectives of the study, the statistical methodology and the potential for addressing the objectives with the smallest number of research participants?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Considerations of Risks and Benefits

(1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC identify the different risks of the research protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC determine whether risks have been minimised?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC determine whether the risks are greater than minimal risk based on a written definition of minimal risk?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC evaluate the probable benefits of the research to the participants?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC evaluate the importance of the knowledge to society that may reasonably be expected to result from the research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC evaluate whether the risks to research participants are reasonable in relation to any anticipated benefits to participants and the importance of the knowledge to be gained to society.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Selection of Research Participants

(1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC review the methods to identify and recruit potential participants?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC review recruitment processes to ensure that the selection of subjects will be equitable in regards to gender, religion, and ethnicity?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC identify the potential of the research for enrolling participants who are likely to be vulnerable to coercion or undue influence (such as children, prisoners, persons with mental disabilities, or persons who are economically or educationally disadvantaged)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC consider the justification for including vulnerable populations in the research?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC consider and require that additional safeguards be included in the study to protect the rights and welfare of the subjects?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC consider the appropriateness of any financial or material incentives offered to participants for their participation in the research?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Privacy and Confidentiality

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC preserve privacy by evaluating the setting in which participants are recruited?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC evaluate the methods for protecting the confidentiality of the collected research data?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Community Consultation

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC review whether the potential benefits of the research are relevant to the health needs of the local community/country?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC review whether any successful study product will be reasonably available to the concerned communities after the research?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC review whether the community was consulted regarding the design and implementation of the research, if applicable?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Safety Monitoring and Adequacy of Insurance to cover research-related injury

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC require, when appropriate, that the research plan includes adequate provisions for monitoring the data collected to ensure the safety of subjects?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC consider whether the sponsors of the research have adequate insurance to cover the treatment of injuries related to the research?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Paediatric Research

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC evaluate the need to obtain the child’s assent?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Informed Consent

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the REC review the process by which informed consent will be obtained (e.g. how do investigators identify potential subjects, where does the informed consent process take place, are potential subjects allowed to take the consent form home and given enough time to ask questions, etc.)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC review which members of the research team will approach potential participants for their informed consent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC ensure that the informed consent document is understandable to the subject population? Suggested ways to assess the consent form might include:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ evaluate the reading level of the consent document</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ have a community member read the consent form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ require investigators to assess subjects’ understanding of the consent form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC waive the requirement to obtain informed consent that is based on written criteria?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the REC waive the requirement for a written signature on the informed consent document that is based on written criteria?</td>
<td></td>
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</tbody>
</table>
Basic Elements of Informed Consent: Does the REC evaluate whether informed consent forms contain the following basic elements of informed consent? (1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A statement that the study involves research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An explanation of the purposes of the research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The expected duration of the subject’s participation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A description of the procedures to be followed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identification of any experimental procedures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A description of any reasonably foreseeable risks or discomforts to the participant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A description of any benefits to the participant or to others that might reasonably be expected from the research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For research involving more than minimal risk, an explanation as to whether any medical treatments are available if injury occurs and, if so, what the treatments consist of or where further information may be obtained.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An explanation of whom to contact for answers to pertinent questions about research.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An explanation of whom to contact for answers to pertinent questions about research participants’ rights.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement that participation is voluntary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A statement that participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Communicating a decision – Approval letter (Maximum 5 points)

Please answer the following questions regarding the approval letter sent to the PI. If no approval letter is sent to the investigator, please skip this section.

Which of the following items are in the approval letter? (1 point each)

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide an expiration date that is one year from the date of the convened REC meeting in which the study was approved.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Require the investigators to submit to the REC as an amendment any changes that occur in the research plan; for example, change in investigators, change in drug doses, change in the sample size, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Require the investigators to report any adverse events or unanticipated problems promptly to the REC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Require the investigators to report any protocol deviations promptly to the REC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Require investigators to use the REC-approved informed consent form that is stamped with an expiration date.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Continuing Review (Maximum 16 points)

Does the REC request a continuing review report from the investigators on an at least yearly basis?  
Yes □ No □ 5 points

If yes, which of the following items are requested in the continuing review report?  

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects enrolled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender and ethnic/religious breakdown of enrolled subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects withdrawn from the research by the investigators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The reasons for withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects who dropped out of the research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The reasons why subjects dropped out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification that informed consent was obtained from all subjects and that all signed consent forms are on file</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number and description of serious adverse events in the previous year (SAEs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>List of any protocol violations or deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any safety monitoring reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the study is completed, submit a final report describing the study results</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REC Resources (Maximum 16 points)

Does the REC(s) have its own yearly budget?  
Yes □ No □ 5 points

If yes, is there a budget for training of administrative staff and REC members?  
Yes □ No □ 1 point

Please check below the physical resources of the REC (check all that apply): 1 point each

- □ access to a meeting room
- □ access to a computer and printer
- □ access to the internet
- □ access to a facsimile
- □ access to cabinets for storage of the protocol files

Have administrative staff been assigned to the REC?  
Yes □ No □ 5 points

If yes: is the person full-time?  
Yes □ No □ 5 points

Is the person half-time?  
Yes □ No □ 5 points
REFERENCES

15. Sleem, H; Moodley K; Kumar, Moni, M; Naidoo, S; Silverman, H. Self-Assessment of the Operations and Functions of Research Ethics Committees in Developing Countries: A Pilot Study. International Association of Bioethics, June 26-29, 2012, Rotterdam, Netherland.
PART V

APPENDIX
24 Review Form

This is a suggested template that can be used by reviewers for the purpose of ethics review of research proposals/protocols. It can be simplified if necessary or adapted to meet the specific needs of local RECs. For example an REC that is exclusively reviewing clinical trials can delete the sections aimed at qualitative research and vice versa.

CONFLICT OF INTEREST STATEMENT

I ________________________________ declare that I have no financial or other involvement or relationship with persons involved in this research project, which may negatively influence my ability to carry out an objective review of this study.

______________________________  ______________________________
Signature                        Date

OR

☐ I do have financial or other competing interests with respect to this project, that may present a potential conflict of interest and I thus request it be allocated to another reviewer.
## SHORT SUMMARY OF PROJECT

### Reviewer Comments

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Introduction, specific aims, literature review</strong></td>
<td></td>
</tr>
<tr>
<td>Is the literature review adequate?</td>
<td></td>
</tr>
<tr>
<td>Are the study aims and objectives clearly specified?</td>
<td></td>
</tr>
<tr>
<td>Is there adequate preliminary data to justify the study?</td>
<td></td>
</tr>
<tr>
<td>Are adequate references provided?</td>
<td></td>
</tr>
<tr>
<td>Is there appropriate justification for this study protocol?</td>
<td></td>
</tr>
<tr>
<td>Why is it important to conduct this study? Will it add important knowledge to the field?</td>
<td></td>
</tr>
<tr>
<td>Why is this study worth doing in this particular setting?</td>
<td></td>
</tr>
<tr>
<td><strong>2. Scientific design</strong></td>
<td></td>
</tr>
<tr>
<td>Is the scientific design adequate to answer the study question(s)?</td>
<td></td>
</tr>
<tr>
<td>Is the scientific design adequately described and justified?</td>
<td></td>
</tr>
<tr>
<td>Does the study involve a placebo? If so, is the need for placebo adequately justified? Could the study be done without a placebo?</td>
<td></td>
</tr>
<tr>
<td>Are study aims and objectives achievable in the given time frame?</td>
<td></td>
</tr>
<tr>
<td>Do the principal and co-investigators have appropriate academic and clinical credentials and experience to conduct this study?</td>
<td></td>
</tr>
<tr>
<td><em>Qualitative research:</em></td>
<td></td>
</tr>
<tr>
<td>- Does the researcher have experience in conducting qualitative research?</td>
<td></td>
</tr>
<tr>
<td>- Does the researcher demonstrate an understanding of the qualitative paradigm and method chosen?</td>
<td></td>
</tr>
<tr>
<td><strong>3. Selection of participants</strong></td>
<td></td>
</tr>
<tr>
<td>Is the choice of participants appropriate for the study question?</td>
<td></td>
</tr>
<tr>
<td>Is the rationale for the proposed number of participants reasonable?</td>
<td></td>
</tr>
<tr>
<td>Is participant selection equitable?</td>
<td></td>
</tr>
<tr>
<td>Are inclusion and exclusion criteria clearly stated and reasonable?</td>
<td></td>
</tr>
<tr>
<td>Is the inclusion of children, pregnant women or other vulnerable groups adequately justified?</td>
<td></td>
</tr>
<tr>
<td>Are adequate safeguards in place to protect the rights and welfare of these vulnerable groups?</td>
<td></td>
</tr>
<tr>
<td>Can the study be done without involving vulnerable populations?</td>
<td></td>
</tr>
<tr>
<td>Will the study target or exclude a particular ethnic or language group?</td>
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</tr>
<tr>
<td><em>Qualitative research:</em></td>
<td></td>
</tr>
<tr>
<td>- Is the method of sample selection appropriate and clear?</td>
<td></td>
</tr>
<tr>
<td>- If the sample size cannot be delineated before the study begins, are a rationale and plan provided?</td>
<td></td>
</tr>
<tr>
<td>- Has the researcher clearly described how they will determine when adequate sampling (saturation) has occurred?</td>
<td></td>
</tr>
</tbody>
</table>

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Has the study population been involved in previous research and/or is the study population currently involved in research to the extent that the current study may present a significant additional burden?

### 4. Recruitment strategy
- Are the methods for recruiting participants clearly explained and appropriate?
- How and by whom will individuals be identified for recruitment?
- Is the location, setting and timing of recruitment acceptable?
- Are screening procedures prior to recruitment acceptable?
- Will any potential participants be in a dependent relationship with the researcher/recruiter? (e.g. Student/lecturer, employee/employer, patient/doctor)
- Has the researcher taken steps to ensure that the participant’s decision to enrol will not be inappropriately influenced by this relationship?

### 5. Research procedures
- Are the rationale and details of research procedures described in sufficient detail?
- Are the research procedures acceptable and in keeping with study aims and objectives?
- Is there a clear distinction between research procedures and standard clinical practice and/or standard care?
- Are the proposed tests/measurements appropriate, valid and reliable to answer the study question in the local context?
- Is there a clear description of plans to inform participants of specific research results e.g. Incidental findings, clinically relevant findings?
- Are those performing the research procedures adequately trained?

### 6. Risk-benefit assessment
- Are risks and benefits (to individuals and/or community) adequately identified, evaluated and described? (Physical, psychological, social, and economic)
- Do risks and benefits stated in the protocol match those described in the informed consent form?
- Are potential risks minimised?
- Are potential benefits maximised?
- Will counselling or support services be available, if required?
- Are potential benefits realistically described and not over emphasized?
- Are risks reasonable in relation to anticipated benefits?
- Are risks reasonable in relation to importance of anticipated knowledge gained?
- Is the risk/benefit ratio acceptable for proceeding with the research?
- Is the population from which study participants are drawn likely to benefit from the research?

### 7. Clinical drug/device trial
- Has the national drug regulatory authority approval been obtained, if required?
| Are the drug or device safety and efficacy data sufficient to warrant the proposed phase of testing? |
| Is the use of placebo adequately justified from both a scientific and an ethical perspective? |
| Are there adequate provisions for safety monitoring including a dsmb? |

### 8. Data analysis and statistical analysis

- Are the plans for data and statistical analysis defined and justified?
- Has the sample size and selection been adequately justified?

*Qualitative research:*
- Is it clear and well-motivated why or how qualitative data collection methods are the most appropriate for analysis?
- Is there clarity in the analytic approach?
- Does the description of the analytic approach indicate how this will allow the researcher to pursue their objectives?
- Has the researcher adequately described how they intend to go about coding and analysis?
- Is there evidence and detail of a conceptual framework?

### 9. Compensation and costs for subjects

- Are there adequate plans to avoid out-of-pocket expenses and costs to participants?
- Is the amount or type of compensation or reimbursement reasonable and well justified?
- If children or adolescents are involved who receives compensation and is this appropriate?

### 10. Privacy and confidentiality

- Are there adequate measures to protect the privacy and ensure the confidentiality of the research subjects?
- Does the protocol describe site-specific measure to protect privacy?
- Does the protocol describe how written records, audio or videotapes, and digital recordings will be secured, for how long, and whose responsibility?
- For focus groups, are participants informed that confidentiality cannot be guaranteed as group members may disclose what we discussed outside the research setting?
- Are activities that could potentially result in notification e.g. Abuse, neglect, potential for harming self or others, addressed in the protocol and IC form?

### 11. Process of obtaining informed consent and assent

- Is the process adequately described? Or has a waiver of informed consent or waiver of documentation of informed consent been requested and adequately justified?
- Are all required elements of informed consent contained in the ICF?
- Is the language level appropriate?
- Does the process minimise the potential for undue influence?
- Does the process provide sufficient time, privacy and an adequate setting for participants to decide?
- Will the ICF be translated into all required languages?
- Is assent required?
12. Other

Is the investigator and research team adequately qualified to carry out/supervise the research?

Does the PI have ‘human subjects protection training’ /GCP?

Is the budget adequate?

Other comments related to the budget?

Are there any administrative deficiencies with the application, such as missing documents?

Has a material/data transfer agreement been submitted if required?

12. At the end of the study

Will post trial treatment be available?

Who will provide this treatment and for how long?

How will communities and participants be informed of significant findings?

How will findings be disseminated more broadly e.g. publishing, presenting etc?

OTHER COMMENTS

Recommendation

☐ APPROVED

☐ APPROVED WITH STIPULATIONS (research can begin subject to certain set pre-conditions – the onus rests with the research applicant to fulfil these)

☐ MODIFICATIONS REQUIRED (Approval will be finalised by the 1st reviewer and Chairperson once satisfied with changes/clarifications.)

☐ DEFERRED or “REFERRED BACK” (NB: the project must serve before the committee again before it can be given “Final Approval” Status.)

Reason/s for above recommendation

REFERENCES

GENERAL INSTRUCTIONS FOR WRITING ADULT INFORMED CONSENT FORMS AND CHILDREN ASSENT FORMS

The following sample consent form is intended to assist with the writing of an informed consent form for research involving human subjects.

This is a sample consent form and pagination will vary according to the actual consent form.

Definitions

Adult: A person who has attained the legal age of majority in the country where the research is to take place.

Children: Persons who do not have the legal age for consent to treatments or to participate in a clinical trial, usually being individuals who are under 18 years in age.

Assent (for children of 7–17 years): is a child’s agreement to participate in research.

The language used in an adult consent form should be in layperson’s terminology, and non-coercive. A practical guideline is that the content should be understandable to a 14-year-old. Sentences should be short and concise, with all initials and abbreviations explained. Avoid using technical terms and non-standardised acronyms (use descriptive language in lay terms). The consent form should be translated into the participant’s local language, and should be a good translation, in order to ensure understanding. It is always advisable to obtain an independent back translation of a translated consent document.
Additional instructions:

1. The title of the consent form is the same as the project title and should appear on the first page, as well as on the signature page.
2. Provide the name and contact details of the principal investigator. Always include a local telephone number and if the study is a clinical trial include a 24 hour contact number.
3. State whether the research sites involve only a local site or multiple sites.
4. Number each page [Page 1 of 4, Page 2 of 4, etc.].
5. Provide space for a version number and date for each consent form, to be entered in the bottom margin of each page. Said version number and date should appear in all correspondence relating to this consent form, in order to allow for identification of the version that has been reviewed and approved. When revisions are made, issue a new consent form version number and date that must be included on the relevant form. Revisions must be approved prior to implementation.
6. Double-side the consent form. The signature page should never stand alone. If the consent form has an odd number of pages, single-side the first page and double-side the remaining pages in order to avoid the occurrence of such a problem.

SAMPLE INFORMED CONSENT FORM

[Use appropriate institutional letterhead]

Project Title
Principal Investigator __________ [MD (OR PhD, etc.)]
Phone number(s) __________________

What you should know about this research study:

- We are providing you with this consent form so that you may read about the purpose, risks, and benefits of the research study in which you are about to participate.
- Routine care refers to the best-known treatment, which is provided with the aim of helping the individual patient. The main aim of research studies is to gain knowledge that may help you and/or future patients.
- We cannot promise that you will gain benefit from this research. As you may be aware, routine care, can have side-effects that can range from serious to minor, which is also true for research.
- It is your right to agree or to refuse to take part in the research, and you may change your mind later.
- Your decision will not affect your routine health care.
- Please review this consent form carefully and ask any questions or raise your concerns regarding the research before you take a final decision to participate or not in the study.
- Your participation in the research is totally voluntary.
Purpose
You are being asked to participate in a research study on [State what is being studied.]. The purpose of the study is to [State what the study is designed to discover or test. If the study is for an investigational drug, for example, you should indicate that the study is to test the effectiveness and safety of the drug concerned.]. You were selected as a possible participant in this study because [State why the participant was selected.]. [Include the expected number of participant/participants in the study in the same COUNTRY and elsewhere.]

Procedures And Duration
If you decide to participate in the study, you will undergo [Describe the procedures as well as their purposes in detail; also how long they will take, and their frequency. You should list and describe both standard and experimental procedures with a clear distinction between procedures that are standard and those that are experimental; especially those that are solely for the purposes of the study. The expected duration should be stated].

Risks And Discomfort
[Describe all reasonably foreseeable risks, discomfort or inconveniences – including health, legal, economic and psychological risks, as well as indicate the the likelihood and seriousness of the potential risks involved. State the nature and type of the risks, if any, to pregnant women. If the risk is significant, add the following section:]

Risks to pregnant women, if applicable
This research may represent a significant risk to your unborn child. If you are a woman, or have childbearing potential, you will undergo a pregnancy test prior to the initiation of the research. If you are pregnant you will be advised that there are different possibilities for study participation. You may choose not to participate in the study at all. Or you may delay this research until you have delivered your child. [If applicable, add/ adapt:] In certain circumstances the research physician may advise that it is safe to participate in the study. This will depend on several factors including the nature of the study, the nature of your illness and the stage of your pregnancy. [If applicable, add:] You may be offered alternative therapy. If you are not pregnant, you will be offered information on birth control procedures to be followed during the course of this research to prevent pregnancy during your research participation. You will also be informed about the danger that the study poses to the fetus. If you do fall pregnant during participation in the study, the study staff will discuss your options regarding your remaining in the study.
Benefits and/or Compensation

[Describe any benefits that may reasonably be expected to derive from the research for the participant/participants and/or for others who stand to be affected by the research. Clearly state whether the benefit is expected to be primarily for others. If benefits are mentioned, add:] We cannot promise or guarantee that you will receive any benefits from this study.

[If there is any compensation for research participation in the study, state the amount that participants may receive therefrom (Note, the remuneration should be in line with the REC approved range of reimbursement). Compensation may include any of the following: free treatment, free medications money, or free transportation. Money may be offered to reimburse expenses, transportation, time, and any other inconvenience. Financial remuneration should never be used as an inducement to participants to assume risks.

Alternative procedures or treatments

[Describe the appropriate alternative courses of treatment or procedures that may be advantageous to the participant. Disclose any standard treatment that may be withheld. State that the potential participant will receive standard treatment, regardless of study participation, as well as that one alternative is no further therapy.]

Confidentiality

If you agree to participate in this study by signing this document, we may disclose the following to [State the persons or agencies to whom the information will be furnished, the nature of the information to be furnished, and the purpose of the disclosure.]. [If applicable, add:] Any information that is obtained in connection with this study that can indentify you will remain confidential and will be disclosed only with your permission. [State who may have access to the study data. If the data from this study are to be supplied to the REC concerned, state that authorised representatives central research offices and sponsors will have access to your medical records for purposes of inspection.] Under some circumstances, the IRB concerned may need to review patient records for compliance audits.

Additional Costs

[Specify the costs the study will bear, as well as the responsibility of the participant. If there is potentially additional costs to the participant because of their participation in the study, such possibility should be disclosed to them herein.]

In the Event of Injury

In the event of injury resulting from your participation in this study, treatment shall be offered by those who are responsible for the study. In the event of injury, contact [You
should provide the name and phone number(s) of the contact person(s) who are available 24 hours a day if you suffer any injury.]

Voluntary participation
Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your future relations with the …………………. [name of institution], its personnel, and associated hospitals [and the named cooperating institution, if any]. If you decide to participate in the study, you are free to withdraw your consent from participating in the study, and to discontinue participation at any time without penalty to yourself.

Additional Elements
[Include a statement of the consequences of a participant’s decision to withdraw from the research and procedures, in order to help ensure the orderly termination of participation by the participant concerned, if appropriate.]

[Include details of the anticipated circumstances under which the participant’s participation may be terminated by the investigator without regard to the participant’s consent, if appropriate, and the procedures to be followed for the orderly termination of the participation by the participant.]

[Include a statement that the participant will be informed if significant new findings develop during the course of the research, which may influence the participant’s willingness to continue participation in the study.]

[The following section must be an integral part of the consent form and can never stand alone, i.e. it can be on the back of the consent form or on part of a page where the aforementioned elements are present.]

Offer to Answer Questions
Before you sign this form, please ask any questions regarding any aspect of this study that is unclear to you. You may, within reason, take as much time as you need to reconsider your participation in the study.

Authorisation
You are making a decision as to whether or not you are willing to participate in this study. Your signature below indicates that you have read and understood the information provided above, have had all your questions answered in relation to the study, and have decided to participate in it of your own free will.
Name of research participant (please print)  Date

__________________________________________  ____________________________

Signature of participant or legally authorised representative  Time

__________________________________________  ____________________________

Relationship to the participant

__________________________________________  ____________________________

Signature of witness  Signature of staff obtaining consent

__________________________________________  ____________________________

(Optional)

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those that have been answered by the investigator, including questions about the research, your rights as a research participant, or the implications of research-related injuries, or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact [Insert name and the physical location details of the REC, together with its landline and cell-phone numbers].

Audio and video recording, and photography [if applicable]

(If audio and video recording, and/or photography are part of the study procedures, describe what will be recorded, and the type of recording to be used, namely audio, video, or photographic. Include details regarding where the photographs and/or tapes will be deposited on completion of the study. Indicate how the tapes will be used. If the recordings are to be used for any other purposes in addition to the research, such as in educational programmes, or as part of a presentation at a professional meeting, provide clear information regarding such use. You may incorporate information regarding providing the participants with the option of hearing the tapes or seeing the photographs prior to their use. If your project does not involve audio, video, or photographic recordings, you may delete this section from the consent document.)
Statement of Consent to be photographed, audiotaped or videotaped

I understand that photographs will be taken/audio/video recordings will be made during the study. (Indicate with a tick (✓) either ‘Yes’ or ‘No’)

I agree to having my photograph taken.

Yes □   No □

I agree to being audio recorded.

Yes □   No □

I agree to being video recorded.

Yes □   No □

[Delete the options above that are not appropriate for this study.]

Name of research participant (please print)  Date

-------------------------------------------------------------------------------------------------------------------------------

Signature of participant or legally authorised representative  Time

-------------------------------------------------------------------------------------------------------------------------------

Relationship to the participant

[This line should not appear on forms that will be given to participants consenting for themselves.]

Name of witness (please print)  Signature

(Optional)

Date  ________________

Name of staff member obtaining consent (please print)  Signature
ASSENT FORM TEMPLATE FOR CHILD PARTICIPANTS

NB! This is only a template and should be carefully and sensitively adapted to meet the needs of the specific group of children participating in your study. Language and style of writing would thus be different for a study recruiting 7 and 8 year olds compared to a study recruiting teenagers.

Please note:

7. Children with the ability to understand the basic concepts of research, must assent to a research study. This is generally possible for children between the ages of 7 to 17 years of age, but these ages are not a fixed rule and some children younger than 7 years of may also have sufficient insight and understanding to give assent for a study.

8. If children refuse assent their refusal should be accepted, even if the parents have consented, although there are exceptional cases where this rule may not apply. The REC should evaluate case by case.

9. This template is specifically developed for 7-12 year olds and should be adapted for adolescents, who may expect more adult type use of language.

10. If the age range of children potentially involve in research are wide, you will need 2 different versions of assent, one for younger children and a more detailed one for adolescents.

11. Adapt this template to suit the needs of your specific project.

12. This assent document must be used in conjunction with a parental information leaflet and consent form. See above for adult consent form, which should be modified for parents.

13. Once your project has been approved and you have a REC reference number, insert the information in the ‘footer’ with the REC number, version and date: e.g. Project No…… Assent template Version 1.1; Date 10/08/09.

14. Assent forms can be made more child friendly by the use of appropriate pictures.
PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM

TITLE OF THE RESEARCH PROJECT: ________________________________

*Insert the title of research project. Simplify if necessary.*

RESEARCHERS NAME(S): ________________________________

ADDRESS: __________________________________________________________________________

CONTACT NUMBER: _________________________________________________________________

What is RESEARCH?
Research is something we do find new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about children and teenagers and the things that affect their lives, their schools, their families and their health. Research also helps us to find better ways of helping, or treating children who are sick. We do this to try and make the world a better place!

What is this research project all about?
*Explain in simple child friendly language. Adapt the information according to age of the age range of child participants that the research targets.*

Why have I been invited to take part in this research project?
*Answer this question in simple language.*

Who is doing the research?
*Identify yourself and explain who you work for and/or why you are doing the project.*

What will happen to me in this study?
*Describe what the participant will be expected to do. Describe all procedures using simple terms and explain any technical or medical term.*

Can anything bad happen to me?
*Use simple terms to explain any possible risks to the child. State if something might be painful or scary to the child. Explain to the child that they must tell his/her parents if they are sick or in pain during the course of the study.*
Can anything good happen to me?

*Only describe known benefits to the subject. You may describe any possible future benefits for other children with similar condition or in similar position. State if there are no known benefits.*

Will anyone know I am in the study?

*Explain in simple terms that the subject’s participation in the study will be kept confidential, but information about him/her will be given to the study sponsor. (NOTE: This information may not be applicable in assent forms for very young children).*

Who can I talk to about the study?

*List those individuals the subject can contact (including their contact details) if he/she has any questions or has any problems related to the study.*

What if I do not want to do this?

*Explain to the participant that he/she can refuse to take part even if their parents have agreed to their participation. Explain that they can stop being in the study at any time without getting in trouble.*

Do you understand this research study and are you willing to take part in it? Yes □ No □

Has the researcher answered all your questions? Yes □ No □

Do you understand that you can pull out of the study at any time? Yes □ No □

_________________________  __________________________
Signature of Child  Date
Glossary

This short glossary contains a combination of commonly used acronyms and terms. Please note that many of the chapters further define terms that are specific or particularly relevant to that chapter. For example the chapter on clinical trials explores the concept of a clinical trial and further defines Phase I to Phase IV trials.

AAREC: African Administrators of Research Ethics Committees
AMANET: African Malaria Network Trust
AU: African Union
AVAREF: African Vaccine Regulatory Forum
Benefits: Benefit applies to the potential of the research treatment to ameliorate a condition or treat a disease. This can apply to an individual participant or to a population
CAB: Community Advisory Board
CBPR: Community based participatory research
CCRT: Community Cluster Randomised Trial
CITI: Collaborative Institutional Training Initiative
CIOIMS: Council for International Organizations of Medical Sciences
COHRED: Council on Health Research for Development
Conflict of interest: In the context of a REC a conflict of interest arises when a member the REC has an interest or affiliation which may negatively influence their ability to evaluate a particular research project or study objectively.
DAIDS: Division of AIDS
DHHS: Department of Health and Human Services
DMC: Data monitoring committee
DMSB: Data monitoring and safety board
Economic risks: The participant incurs direct or indirect financial costs due to participation in the research project.
EDCTP: European and Developing Countries Clinical Trials Partnership
Ethical Review: Ethics review is a specialised process designed to evaluate the ethics of proposed research involving human participants.
ERB: Ethical Review Board
ERC: Ethics Review Committee
EMA: European medicines agency
EU: European Union
FDA: Food and drug administration
FHI: Family Health International
FIC: Fogarty International Centre
FWA: Federal wide assurance
GEEI: Global Ethics Educative Initiative
GCP: Good clinical practice
GWAS: Genome wide association studies
HRE: Health research ethics
HRWeb: Health Research Web
ICH: International Conference on Harmonization
IMS: Information management system
Insurance of clinical trials participants: The financial compensation arrangement plan for research participants in case of injury as a result of participation in research, especially clinical trial.

IRB: Institutional Review Board
IEC: Information, education and communication
KEMRI: Kenya Medical Research Institute
LMIC: Low- and middle-income countries
MARC: Mapping African Research Ethics Review Capacity
NHREC: National Health Research Ethics Council
MRAs: Medicines regulatory authority
NDRA: National drug regulatory authority
NIAID: National Institute of Allergy and Infectious Diseases (USA)
NIH: National Institute of Health, United States of America
OHRP: Office for Human Research Protection
ORI: Office of Research Integrity
PCT: Placebo controlled trial
PHRP: Protecting Human Research Participants
Physical risks: Include minor or serious bodily harm that may be temporary or permanent. The risks may occur immediately or be delayed and is due to the participation in the research study.
PLWH: People living with HIV
Principal Investigator (PI): A principal investigator is a suitably qualified scientist who leads the research team and ultimately takes responsibility to ensure that the research is conducted with ethical and scientific integrity.
Protocol amendment: A protocol amendment is a written description of a proposed and planned change to a research project usually initiated by the investigator or sponsor.
Protocol violation: A protocol violation means that the investigator has, for whatever reason, not kept strictly to the protocol. All protocol violations must be reported to the project sponsor and the REC (especially in the case of self-initiated research.)
Psychological risks: The participant may suffer emotional discomfort such as anxiety, shame or may affect the perception of self or may cause thought and behaviour aberrations.

REC: Research Ethics Committee refers to a multidisciplinary, independent body responsible for reviewing research proposals involving human participants to ensure that their dignity, rights and welfare are protected.
Research participant: a person who takes part in a research study and hence serves as a data source for research.
Research protocol or research study is a written document that describes the proposed research in detail, starting with a literature review and background, then the justification for the project, aims, objectives and methodology, a description of ethical concerns and a data analysis plan.
Research vulnerability: a term used to describe individual participants or communities that may not be fully able to protect their own interests when participating in research. They are thus at risk of being exploited.
RHInnO: Research for Health and Innovation Organiser
Risks: Risk within the context of research is an estimation of the probability of physical, psychological, social, or economic harm occurring as a direct result of an individual or a community's participation in a research study.
SAE: Serious adverse event
SARETI: South African Research Ethics Training Initiative
SMP: Safety-monitoring plan
Social risks: The participant may be exposed to discrimination or social stigmatisation in the work place or social life or when applying for insurance.
SOPs: Standard Operating Procedures are written sets of documents describing operational processes in detail.
TM: Traditional medicines
TRE: Training Research Ethics
TRREE: Training and Resources in Research Ethics Evaluation
UK: United Kingdom
UN: United Nations
UNECA: United Nations Economic Commission for Africa
USA: United States of America
WAB: West African Bioethics
WHO: World Health Organizations