



## **POLICY BRIEFING**

### **CHALLENGES FACING DEVELOPING AND TRANSITION COUNTRIES IN ESTABLISHING AN EFFECTIVE SYSTEM OF RESEARCH ETHICS INFRASTRUCTURE**

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## **CHALLENGES FACING DEVELOPING AND TRANSITION COUNTRIES IN ESTABLISHING AN EFFECTIVE SYSTEM OF RESEARCH ETHICS INFRASTRUCTURE**

- ❖ This briefing is a synthesis of discussions and conclusions at the 8th Global Forum on Bioethics in Research. It is intended for members of Research Ethics Committees, policy-makers, researchers and others engaged in the planning and implementation of health research.
- ❖ The synthesis highlights issues that need to be resolved in understanding how to establish an effective research ethics infrastructure, which promotes and safeguards the welfare of research participants.

There is worldwide consensus that Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) are needed to protect the rights and well-being of human participants in health research. But making this a reality remains a formidable challenge.

Addressing this challenge is the main goal of the Eighth Global Forum on Bioethics in Research. More than 100 experts in bioethics, medicine, and policy-making from some 35 countries met in Vilnius (Lithuania) to discuss how to operationalize Research Ethics Committees in developing and transition countries, and the role of such committees in reviewing research protocols involving participants with mental health disorders.

### **ACTION POINTS**

- Sound composition of an REC and financial support to its secretariat are crucial for the conduct of competent and independent review.
- The protection and promotion of the freedom to research should be limited by the requirement to protect human participants. This should be the starting point of any legislation concerning research on humans.
- Any considerations about how to improve the review and conduct of clinical trials, such as requiring that RECs include members with expertise in mental disorders, must balance the need for ethical oversight with minimizing burdens that may unnecessarily inhibit research from being carried out.
- Where theoretical problems, such as those concerning the capacity to consent, have been resolved, tangible policies and procedures still need to be put into place in order to implement these solutions. Such policies and procedures may need to be adjusted to take account of different social, cultural, and economic contexts.
- A reasonable and defensible justification for the inclusion of vulnerable people in research must be provided in the research protocol, as well as the measures taken to protect their rights and to safeguard their welfare.

## OPERATIONALIZING RESEARCH ETHICS REVIEW

### 1. ESTABLISHMENT, COMPOSITION AND ORGANIZATIONAL ASPECTS

The need for ethical oversight of biomedical research became clear following a series of revelations concerning medical trials that violated the rights and damaged the welfare of human beings. In response, various international guidelines were developed, the implementation of which was intended to prevent further abuses of research participants (see Table 1, p9).

However, there is still significant debate and controversy regarding their implementation. Much of this debate centres on questions about how an REC or IRB should be structured, composed, and administered to achieve the required protection of research participants before, during, and after the research takes place.

These questions become particularly pressing when RECs have limited funds, lack capacity in research ethics review, are poorly managed, are without formal written Standard Operating Procedures or have no follow-up mechanisms. Can such RECs carry out a meaningful ethical review?

#### ETHICAL ISSUES

- **Over-protecting research participants**

The main purpose of an REC is to protect the interests of research participants. However, in research where the chance of harm to participants is low, over-vigilance may slow the research process. This may impede funding, or leave research proposals out of date. Similarly, when more than one REC reviews a research protocol, there may not be much improvement in the protection of research participants. RECs often have more protocols to review than time in which to review them. Is there a need for more RECs, or can the review process for some studies be expedited without risking the welfare of research participants?

#### KEY ISSUES

- **Should governments aim to establish regional RECs or IRBs?**
- **What is the right distribution of scientists, health care and social sciences professionals, lawyers, and lay members in an REC? What is the appropriate profile for lay members?**
- **What national policy instruments can be used to expand REC review to include both private and public research?**
- **Are RECs over-regulating research and thereby stifling rather than promoting ethical research?**
- **Financing RECs and reimbursing secretariat and members: should their service be voluntary, or should they be paid for their contributions?**
- **One tier vs. two-tier models of ethical review for multi-centre trials: which is preferable?**
- **What are the relationships between RECs from developed and developing countries? What should they be?**
- **What should be the relationship between RECs and other bodies responsible for regulating research, e.g. between RECs and so-called "competent authorities" like state drug agencies which issue approvals for clinical trials?**
- **Legal status of research protocol review by RECs: should the approval be legally binding or should it rather serve as a recommendation?**

- **Composition of the REC**

Health research involving individuals or communities raises complex scientific, environmental, ethical, legal, and cultural issues. REC members have a responsibility to address each issue, in order to make an informed decision on the ethical soundness of the research protocol. How then should an REC be composed in order to competently review complex research protocols?

- **Multi-centre studies and host country ethics review**

There has been substantial debate about the quality of ethical review in developing countries, with most of the controversies centred on political commitment, legislation, and capacity building. One danger is that trial hosts in developing countries may place the securing of international funding ahead of the interests of the research participants in research and the local community. Some institutions or community members may even exert pressure for the approval of research, because it would bring jobs, improved infrastructure, money, or political goodwill to the community.

Who is responsible for improving the conditions (specifically monitoring, supervising, training, and facilitating communication between local, national and international RECs), under which the ethical review of research protocols is conducted, the national government, the local institution, the international community, or the local REC itself?

## **ETHICS GUIDELINES**

The World Health Organization *Operational Guidelines for Ethics Committees That Review Biomedical Research* (WHO/TDR/PRD/ETHICS/2000.1) has provisions regarding the quorum of an REC, though there is no clear delineation in terms of the composition and the ratio of scientific/non-scientific/non-affiliated members (TDR, 4.5). CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, 2002 states that it is *presumed* that REC membership represents the *cultural and moral values of the community* (CIOMS guideline, 2).

## **2. DOMAIN AND COMPETENCIES**

International guidelines on the ethical principles governing the bodies that review research protocols involving human participants (independence, competence, pluralism, and transparency) have won universal assent (WHO/TDR/PRD/ETHICS/2000, 2002). However, there is not general agreement on the specific domains and competencies of an REC. This may be partly due to the fact that there is not a broad consensus on what counts as research on human beings, or because the function of the REC is not clear (for instance, is it only to review the ethical soundness of a research protocol, or is it to review the scientific merit as well?)

Research related to health is extremely varied. There are many possible sources of data, including paper records (documental research) and biological samples

### **KEY ISSUES**

- **What sorts of studies should be considered by RECs?**
- **How should "research" be defined for the purposes of REC review?**
- **Where is the boundary between clinical research and clinical/managerial quality improvement projects?**
- **How should social science research, e.g. questionnaires, be reviewed?**

(biobank-based research), and many methodologies, such as comparison (randomized controlled clinical trials), observation (descriptive, cohort, case-control, cross-sectional, participant observation), inference (descriptive or analytic research), and intervention (physical, chemical, psychological, social environment). Determining which of these require ethical review will determine the domain of RECs.

Further, many health research projects are multidisciplinary, extending from the basic biological sciences all the way to social sciences research, they may also be multinational. All of these complexities add new challenges to the way in which ethical principles are applied and how RECs should operate.

Under such circumstances, what if one local REC finds a multi-centre study ethically sound but has neither the expert capacity to judge the relevance of the research against the health priorities set at the national level, nor the capacity to monitor the ongoing research? Who should be responsible for the final protection of research participants: the local REC, the sponsor REC or the local research governance framework?

## **ETHICAL ISSUES**

- **Different notions of research ethics**

One of the challenges posed by multidisciplinary studies in health research is the question of how health research ethics is understood by researchers from two different traditions: social science and biomedicine.

Each approach has different concerns and requirements. In the former, anthropologists and sociologists are more concerned with the political and social implications of health research. In the latter, physician-researchers are more troubled by issues of informed consent and respecting of an individual's autonomy.

When conducting a health research project, should both traditions be measured by the same ethical standard? What differentiates "research" from a practice intended to improve care, and to what extent should quality improvement activities be submitted for REC review? Should harmless research projects conducted by research students, which involve human research participants, be subject to a full review by an REC? Should all projects that involve human participants be treated as "research" and thus be subject to ethical review?

- **Should student research projects be reviewed by the same process and standards as non-student research?**
- **Should the domain of RECs include the monitoring of ongoing research?**
- **How and where should specialized technical expertise be obtained?**
- **Should the scientific quality of protocols be part of the domain of a REC, or should this be left to another body?**
- **Are RECs competent to evaluate the insurance and financial contracts of research projects sponsored by pharmaceutical companies?**
- **What measures can prevent "rubberstamping" or "bullying" in those cases when RECs do not have in-house capacity to judge complicated trial protocols?**
- **How should conflicts between patient care and research interests, be resolved in cases of clinical trials sponsored by pharmaceutical companies?**
- **How should conflicts of interest be resolved in evaluating protocols from sponsors who also contribute to salary?**
- **How should conflicts of interest related to evaluating research projects of colleagues from the same institutions be treated?**

- **Specialized technical expertise**

Biomedical research can involve human research, in order to minimize any potential risks posed to human participants, the research protocol must be both scientifically valid and ethically sound.

The assessment of scientific validity involves the review of the project's rationale and design, and requires that it clearly contribute to the production of new knowledge. Ethical soundness means that the research participants' rights and welfare are safeguarded; for example, there is an informed consent process, and the participant's privacy and confidentiality are duly safeguarded.

However, there are also research protocols which bring up additional issues such as the question of equipoise, the value of the research given local or national priorities for research, the availability of other treatments related to the condition being studied, and the appropriate insurance and financial contracts for the research. In such cases, should RECs request the advice of outside technical experts? Or should it be part of the REC's competency?

- **Minimizing conflicts of interest**

RECs naturally incur costs, for example, through process review, professional time investment, and physical location. However, reimbursing REC members for these costs may lead to conflicts of interest, depending on who reimburses them, and how much they receive. This risk is increased when the research is conducted in low-income countries, and the research sponsors are from wealthy countries.

If an REC is financed, should its members be compensated, and if so, how? Should research participants be compensated, and if so, how? Which is the best way to fund RECs: charging research sponsors the costs of review, channelling funding from multiple sources through a single administrative body, developing a fixed fee structure, requiring in-kind donations, or using institutional resources?

## **ETHICS GUIDELINES**

According to the Declaration of Helsinki (Paragraph 13), an REC's role is to consider, comment on, guide and conduct follow-up of research protocols. According to CIOMS (Guidelines 2, 3) it is to provide scientific and ethical review, to monitor research protocols, and to ensure that the research protocol is responsive to the priorities and needs of the place where the research is carried out. The Declaration of Helsinki, states that the scientific and the ethical review of a research protocol do not require separate committees (Paragraph 13). CIOMS does however state that a separate committee for scientific review might be required (Guideline 2).

In terms of funding, the Declaration of Helsinki states that RECs should be independent of any type of undue financial or political influence (Paragraph 13) and WHO guidelines maintain that *all reimbursement for work should be recorded and made available to the public* (TDR, 4.3.2). CIOMS states that the REC may receive money for the activity of reviewing protocols, *but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol* (CIOMS guideline 2), and stresses that sponsoring countries have a responsibility to support REC capacity building in the countries that might need it (Guideline 20).

### 3. ETHICS OF MENTAL HEALTH RESEARCH

According to the World Health Organization there are over 450 million people in the world with mental, neurological or behavioural problems. Mental health problems are estimated to account for 13% of the global burden of disease (WHO, 2005). Mental health research should therefore be a priority.

In general, the same ethical requirements apply to mental health research as to other biomedical research. There are not ethical issues unique to mental health. Likewise, special considerations about research in resource-poor settings apply equally to mental health research in such settings.

However, people who suffer from mental health disorders are often thought to be particularly vulnerable. This may be a product of problems related to their medical condition, for example, where the condition reduces their capacity to make autonomous decisions. It may also result from social conditions, since people with mental disorders are disproportionately likely to be poor, stigmatized, and the victims of human rights abuses. Either way, particular care is needed to ensure that mental health research is conducted in a manner that protects its participants.

#### ETHICAL ISSUES

- **Trial design**

There are a number of continuing disputes regarding the standard of care offered to participants in research. One such dispute concerns the use of placebo-controlled trials in situations where there already exists a standard treatment for a condition (Helsinki, Paragraph 29; CIOMS, introduction, guideline 11).

It is generally considered unethical to use a placebo-control when testing a new treatment for a condition for which a standard treatment already exists, rather than using the treatment as an active-control. Research participants would otherwise be subject to an unnecessary risk of harm. This is even worse when placebo-control could bring about permanent damage or irreversible deterioration to the study participants.

However, it is not unusual for certain psycho-active drugs to fail to show superiority to placebo. This means that active-control trials may seem to show that an experimental drug is equivalent in efficacy to the current standard treatment, when the explanation for their equivalence is in fact

#### KEY ISSUES

- **What is the status of placebo-controlled trials involving participants with mental disorders?**
- **Which is the appropriate standard of care for participants in mental health research trials?**
- **When is it permissible to enrol people who cannot give informed consent into mental health studies, and who may act as their decision-maker?**
- **From the point of view of researchers and research ethics committees, what, if any, are the major ways in which mental illness itself differs from other health problems?**
- **What, if any, are the main ethical implications for research of the problems with capacity and competence that may be associated with mental disorders?**
- **Should there be special precautions and/or procedures for the ethical conduct of research on persons with mental disorders who have diminished capacity and/or competence? If so, what should these special precautions and procedures be?**
- **Are there special issues in the research of mental disorders that arise in developing country/under-resourced settings? If so, what are these and what additional measures do they require?**

that neither was better than a placebo would have been. Increasing the power of an active-control trial sufficiently to rule out this possibility may require an impractically large number of participants, and will, in any case, put a greater number of participants at risk.

In resource-poor settings, participants may have to join a placebo-controlled trial as it may be the only way to get a chance to receive effective treatment. However, there is an important difference between the choice to participate in a clinical trial by someone who can access treatment elsewhere, and the same choice made by someone who cannot.

- **Informed consent**

A person's capacity to consent is a matter of their fulfilling the criteria for being able to give informed consent. A person's competence is a legal determination of their ability to consent. Many people with mental disorders retain the capacity and competence to give informed consent. Others may lack or be losing them.

Where someone has a diminished ability to consent, they may need assistance to exercise as much autonomy as possible. Where they lack the ability, a proxy decision-maker must accept or decline trial participation on their behalf. Ethical questions arise regarding when it is permissible to enrol people who cannot give informed consent into mental health studies and also about who may act as their decision-maker.

Difficulties with consent are one way in which people with mental disorders may be considered especially vulnerable research participants, but there are several others. Participants' capacity of to give informed consent may vary during the course of treatment, people who suffer from certain illnesses are stigmatized in some communities, participating in research runs the risk of revealing their condition to other people in the community and thereby leading to harm, even where stigma is not an issue, questions of privacy may arise with regard to personal information that is revealed during research or care.

### **ETHICS GUIDELINES**

The World Medical Association's *Declaration of Helsinki* and CIOMS' *International Ethical Guidelines for Biomedical Research Involving Human Subjects* agree that consent to research on individuals whose capacity and/or competence to consent is impaired should be obtained from a proxy representative. The goal of such research should be the promotion of the health of the population that the research participants represent. Further, research on these participants is justified only if it cannot be carried out on individuals who can give adequate informed consent (Declaration of Helsinki, Paragraph 24, 26; CIOMS guidelines 9, 13, 15).

The World Psychiatric Association's *Madrid Declaration* gives guidelines on the ethics of psychiatric practice. This may have implications for what is permissible in mental health research, depending on the extent to which the duties of psychiatrists as personal physicians are also duties of psychiatrists as mental health researchers.

**TABLE 1. RESEARCH ETHICS PROVISIONS AND CONFIGURATION**

<b>Guidance</b>	<b>Event</b>	<b>Key Provisions for research ethics</b>	<b>Importance</b>	<b>Source</b>
Nuremberg Code (1947-1949)  -made of 10 principles-	Trial. Set of principles for the judgement of Nazi physicians' experimentation on concentration camp prisoners during the Second World War	Principle 1: voluntary consent before the experiment begins Principle 2: favourable risk-benefit ratio Principle 9: freedom to withdraw from experiment	First international code of research ethics	Nuremberg Military Tribunals
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979)  -made of 3 broad ethical requirements-	Scandal. The Tuskegee Syphilis Study (1932-1972)	1. Respect for persons: informed consent adapted to the subject's capacities 2. Beneficence: appropriate risk/benefit ratio, minimizing harm and maximizing benefits 3. Justice: equitable selection of research participants, vulnerable populations are not to be targeted for risky research, and fair distribution of research's benefits	Deliberation about the ethical principles which should underlie the conduct of research involving human participants	USA National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research
Declaration of Helsinki (1964, 1975, 1983, 1989, 1996, 2000, 2002, 2004)  -made of 32 ethical precepts-	Medical research. Physicians and physician-researchers, seeking the protection of research participants' welfare without prejudice to the conduct of research and society's interest	(1964) Paragraph 6: distinction between clinical therapeutic research and non-therapeutic biomedical research (1964) Paragraph 8: proxy consent with vulnerable participants (1982) Paragraph 13: independent research ethics committees (2000) Paragraph 29: standard of care	First global federation of national medical associations, whose ethical provisions have been endorsed by all international guidelines as the cornerstone of ethical research	World Medical Association (WMA)
International Ethical Guidelines for Biomedical Research Involving Human Subjects (1982, 1993, 2002)  -made of 21 guidelines-	Declaration of Helsinki applied to low-income countries and countries in emerging conditions challenged by the severe impact of HIV/AIDS, multi-centre studies, and the absence of research ethics training	Guideline 1: morally acceptable research within the local communities Guideline 3: sponsor and host countries responsible for ethical review Guideline 10: research as responsive to population's needs and priorities Guideline 20: ethical review, capacity-building Guideline 21: compensation for research-related injuries	Internationalisation of ethical guidelines to protect research participants in resource-poor settings, against potential abuses or exploitation	Council for International Organizations of Medical Sciences (CIOMS) and The World Health Organization (WHO)
UNESCO's Declaration on Bioethics and Human Rights (2005)  -made of 28 articles-	Ethical guidance in health and genetic research to protect biodiversity, indigenous communities, cultural diversity, and future generations	Article 14: social responsibility and health Article 19: ethics committees to assess ethical, legal, scientific, technological and social issues of research	For the first time member states of the UN committed themselves to the fundamental principles of bioethics in a single, harmonised document	United Nations Educational, Scientific and Cultural Organization (UNESCO)

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