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ETHICS IN HUMAN AND ANIMAL EXPERIMENTS

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Introduction

Research ethics can be simply defined as **norms of conduct** that distinguish between acceptable and unacceptable behaviour encompassing all aspects of research such as planning, conduct, and reporting of results. Application of research ethics is most developed in the field of biomedical research and this will be the focus of this chapter. However, the researcher should be aware that different ethical issues would arise in conducting research in the humanities and social sciences, in particular for studies in areas such as ethnography and anthropology.

The history of modern day 'codes' of research ethics dates back to the Declaration of Helsinki, first developed by the World Medical Association (WMA) in 1964 and updated many times, most recently in 2008[1]. This is a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. Widely regarded as a cornerstone document in the ethics of human research, this declaration has formed the basis of most subsequent documents guiding research practice. For instance, the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* developed by the Council for International Organizations of Medical Sciences (CIOMS) in 1982, more aptly reflected conditions and needs in the changing context of modern day international collaborative biomedical research[2]. The assurance that research conducted by an institution is ethical is achieved by obtaining ethics approval for all research proposals involving human or animal subjects from an institutional review board (IRB) or ethics review committee (ERC).

Why do you need to know about research ethics?

Any person embarking on a research project should have a basic knowledge of what constitutes ethical research. A researcher should be aware of the ethical policies and practices which are applicable to the intended research, as ignorance will not be considered an acceptable excuse for conducting ethically questionable studies. Furthermore even if part of a research project is conducted in an unethical manner, this would reflect upon the integrity and the value of the study as a whole. The starting point for putting ethical guidelines into practice is the formulation of the research proposal. There are some key ethical issues which should be addressed, using accepted strategies on how to fulfill ethical principles. It follows, that the same principles will be considered by the reviewer who evaluates your proposal.

Issues in Human Research

It is imperative that careful consideration is given to any research involving human subjects. Research work of this nature should always be carried out according to a prior approved protocol adhering to applicable laws as well as national and international guidelines. In a broader sense, the study should be in line with the research priorities of the country with the potential to be translated into products, policies and programmes for improving the health of vulnerable populations.

All research involving human participants must be conducted in a manner that respects the dignity, safety and rights of research participants and that recognizes the responsibilities of researchers[3]. The framework used in the analysis of research on human participants is based on four basic tenets of medical ethics:

1. Autonomy - the patient has the right to refuse or choose his or her treatment
2. Beneficence - a practitioner should act in the best interest of the patient
3. Non-maleficence – the primary consideration should be not to harm the patient
4. Justice – ensuring fairness and equality

Building up on these principles and taking their scope of application into consideration, there are eight benchmarks on which present day biomedical ethics guidelines are based [4, 5]:

1. Scientific and social value

A research study should demonstrate social and scientific value through generation of knowledge, which would lead to improvements in health and wellbeing. Even in basic laboratory research it is desirable to highlight how the knowledge generated could lead to applied and translational research. This will also be a criterion used by funding agencies in prioritizing disbursement of limited resources. Ensuring a study meets this requirement would also mean that the risk of exploitation of the participants is minimized.

2. Scientific validity

A research study must be based on clear scientific objectives, be designed using recognized methods and principles, follow good clinical or laboratory practice, have an acceptable plan for data analysis and be feasible. Further, the researchers should be adequately qualified and experienced to carry out the intended study. Researchers often tend to be taken by surprise when questions on scientific methodology are raised at ethics review meetings. The view that scientifically unsound research is unethical is based on the premise that such studies could lead to exploitation of participants and use up limited resources as well as generate questionable results.

3. **Fair subject selection**

   Selection of participants for research should primarily be guided by scientific goals. This applies to formulating specific inclusion and exclusion criteria as well as to selection of the community or group from which actual recruitment would take place. If a vulnerable population (e.g. those socially disadvantaged due to illiteracy or economic status and those with limited autonomy such as prisoners) is chosen as the study subjects, this should not be due to mere convenience and the researcher should be able to justify such selection. Especially in the light of clinical research, fair subject selection strives to ensure that groups who bear the risks of research are in a position to enjoy its benefits and conversely those who may benefit share some of the risks.

4. **Favourable risk-benefit ratio**

   Applicable mostly in the context of clinical research, this denotes that potential risks to participants should be minimized, the anticipated benefits to research participants and communities should be enhanced and the benefits should be proportionate to or outweigh the risks. Non medical benefits to participants, such as payments received, are not considered in a study's risk-benefit ratio. A low risk study which does not directly benefit the participants can still be ethical when the study is designed to potentially benefit society.

5. **Informed consent**

   The principles of informed consent are three-fold. First, the participant should be informed about the research. This includes information on the purpose of the study, the participant's role, risks and benefits and alternative options such as refusing to participate. Second, the information must be understood in the proper context and requires delivering the information using the local language, in a culturally appropriate manner. This may mean obtaining the consent of village elders or the head of the household in some instances. Third, the subject's decision to participate must be voluntary without any undue external influence.

   In certain instances such as the mentally handicapped and unconscious patients the participant will be deemed incompetent to give informed consent. Further, by law, children and teenagers under age 18 are not old enough to give informed consent. In these situations consent should be obtained from a competent family member or guardian. In addition, children or teenagers must also agree to participate, which is known as assent. The lower age limit for obtaining assent and the procedure is variable and is dependent on factors such as literacy rate.

6. Respect for potential and enrolled participants and communities

Research participants should have their privacy and their dignity protected and their wellbeing monitored. This is carried out by measures such as ensuring confidentiality, allowing participants to withdraw from the study at any time without a penalty, providing them with relevant new information as the study progresses and monitoring their welfare. Designing the research in consultation with stakeholders in the community will help the smooth conduct of the study.

7. Collaborative work

The complex scientific questions that face us today often require interdisciplinary or multidisciplinary approaches. Collaborators in such an instance could be researchers of a number of institutions or independent researchers within one country or from a number of countries. Ethical concerns arise especially in international collaborative research which involves a lead researcher in a developed country. Comprehensive guidelines are available which address issues such as the rights of researchers in the developing country, transfer of research material, adequate justification for conduct of the study in the host country and benefits to the host country[6]. Safeguards should be adopted to prevent issues such as biopiracy.

8. Independent review

A research proposal should be reviewed by a group of people not connected with the research (in this case the IRB/ERC) for any relevant ethical issues to be identified in an impartial manner. This is also important for building society's trust in research.

9. Conflicts of interest

These arise when a researcher has personal interests or obligations which conflict with the paramount aim of answering the study question. If conflicts of interest do exist, the objectivity of the researcher and the integrity of the results can come into question. Therefore it is important to address conflicts of interest up front and discuss how to avoid potential lack of objectivity.

10. Data integrity

The ethical practices of a researcher are a continuum and must be reflected in all related activities. A researcher must collect, accurately record, and store data from experiments. Research should be reproducible, and others should be able to view the data from an experiment and arrive at the same conclusions. Data fabrication (making up data or results), falsification (manipulating research materials, equipment, or processes, or changing or omitting data or results) and plagiarism (appropriation of another person's ideas, processes, results, or words without giving appropriate credit) are considered as research misconduct and dishonest practices.

11. Authorship

This is the process of deciding whose names belong on a research paper. Often a research study would involve collaboration and assistance from several experts and colleagues. A key question would be to decide which of these contributions require joint authorship and which require acknowledgement. Responsible authorship practices should be based on internationally accepted guidelines[7].

12. Payment or undue inducement

It is not unethical for a researcher to pay participants an amount of money that is based on their time and inconvenience (e.g. travelling expenses). However, when money is offered to participate in a research, it may lead an otherwise unwilling person to take on the task, ignoring potential risks. This is not an issue confined to the participant alone, as researchers, in large scale sponsored studies, may also receive large payments for subject recruitment which can affect objectivity and attention to patient safety.

13. Peer review

This is the process in which an article submitted to a journal for publication is reviewed by experts in the field for its importance, usefulness, relevance, methods, completeness and accuracy. This process is governed by confidentiality where the reviewers and authors are blinded for details on identification. Further, the reviewer should not have conflicts of interest which can affect fair evaluation of the article. Conflicts may take the form of financial interests, the research being similar to the reviewer's own research endeavors or personal relationships with the author.

Issues in Animal Research

Animal research, for the purposes of these guidelines, is defined as *in vivo* research performed on laboratory animals to develop knowledge that contributes to improvement of health and well-being of humans as well as other animals. The humane and effective use of animals is guided by the 3R concept which is described briefly below:

- Replacement: Refers to replacement of animals with methods that do not require animal use, for example the use of tissue culture or the use of computer modeling or substitution of a lower species which might be less sensitive to pain and distress.

- Reduction: Refers to reduction of the number of animals that are part of an experiment. However this should not compromise statistical integrity or the applicability of the results of the study.
- Refinement: Refers to the improvement of experimental techniques in order to minimise pain, distress or other adverse effects and/or enhance the animals' well-being.

Experience in handling animals is a prerequisite for conducting animal research. The optimum welfare of the animals, identification of humane end points to prevent unnecessary pain and suffering and justification for use of vulnerable groups (e.g. stray animals), are some of the issues to be considered in formulating an acceptable proposal[8].

Emerging Fields

In the present era, with increasing opportunities for interactive research, newer techniques and methodologies are not beyond the local researcher. Researchers embarking on such fields of study (e.g. genetic research, research on stored tissue or biobanking, stem cell research, use of electronic information systems) may find that the guidelines in this country are not very clear as they are still being developed or refined. In the case of clinical trials the DRA (Drug Regulation Authority) has limited clinicians for only phase three and four studies. Research on herbal medicine is another emerging field where guidelines are hazy. In such instances the researcher can be guided by available international guidelines. Support and guidance can also be received from the ERC to which the proposal has been submitted for ethics approval.

Submitting a Research Proposal for Ethics Review – some FAQs

Does my research need ethics approval?

On a theoretical basis, some studies which bear minimal risk such as anonymous audits do not require ethics approval. However, in the present day, any reputed journal requests for evidence of ethics approval at the time of accepting a submission for publication. Thus it is good practice to subject your research proposal for ethics review regardless of the type of study.

When should I apply for ethics review?

An application for ethics review should be submitted at least two months ahead of the planned date of commencement of the study. Since an ERC would meet only once a month, this leaves adequate time for the proposal to be reviewed as well as for the researcher to address any revisions. It should be noted that your application will not be accepted if the study has already commenced or is completed.

Where should I apply?

There are several ERCs affiliated to the Sri Lanka Medical Association, state universities, State Hospitals, Professional Colleges and Associations and other institutions which are members of the Forum for Ethics Review Committees in Sri Lanka (FERCSL). Researchers belonging to an institution should obtain ethics approval from the institutional ERC, as the ERC acts as the guarantor of ethical research to the general public.

Is there a fee involved?

Yes. This is variable depending on the particular ethics review committee. Generally a concession is made if the principal investigator belongs to the same institution as the ERC, whereas studies where the principal investigator is not affiliated to the institution or sponsored research will be charged a higher fee.

What happens after I make a submission?

Your proposal may be exempted from review or undergo expedited review by the executive committee of the ERC or be reviewed by the full ERC depending on the issues to be addressed. The proposal may be accepted as it is, require minor or major revisions or be rejected. The ERC will always provide you feedback and will assist you to meet the requirements for revision.

What are the documents to be submitted for review?

In addition to the research proposal other supporting documents will be requested by the ERC. These commonly include information sheets and consent forms for the participants (with appropriate and accurately printed Sinhala or Tamil translations) and questionnaires. CVs of the investigators will be required to determine if the investigators have the competence, training and qualifications to conduct the research reliably and safely. A Material Transfer Agreement will be requested when biological samples are sent out of the country during the course of the research.

Amendments, protocol deviations and further follow-up

The ERC will request the researcher to submit progress reports at stipulated time intervals. Ethics approval has to be renewed at the end of each validity period until the completion of the study. The researcher is expected to inform the ERC of any amendments or deviations from the study and seek approval for these changes.

Finally, the aim of this chapter is to promote awareness and understanding among young researchers, of the standards and norms of responsible conduct of research. Often there are no absolutely right or wrong answers as to how a researcher should act. What is most important is that you strive to make the best possible decisions in a given situation.

Practice of ethical values in the conduct of research is a continuous learning process and the onus is on the young researcher as well as on his or her supervisors to cultivate these values, including undergoing suitable training in research ethics.

References and Further Reading

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