IS MY CLINICAL RESEARCH ETHICAL?

– CORE CONCEPTS IN THE ETHICS OF CLINICAL RESEARCH

By Chua Shunjie and Dr T Thirumoorthy

MANY MEDICAL students today are engaged in the area of clinical research as a result of the current trend to move clinical questions from the bedside to the laboratory bench. When patients and their personal data are involved in the research process, there will inevitably be ethical challenges and dilemmas. Therefore, we offer a review of the core ethical concepts in clinical research in the format of a concise checklist beyond institutional review board requirements, for the aforementioned students as well as all others doing research.

Definition

Research is defined as a class of activities designed to develop generalisable knowledge, which consists of theories, principles or relationships that can be corroborated by accepted scientific observations and inferences. However, clinical research often has an important therapeutic component. Hence, it is important to differentiate clinical research from clinical therapy or practice as they have different purposes, priorities and methods.

Fundamental ethical principles in research

The ethical principles governing the conduct of medical research involving human subjects are universal and should not differ significantly purely based on the medical specialty or geographical location. The two basic ethical justifications for clinical research that are universal can be summarised as:

1. The ethical duty to alleviate human suffering from diseases and ill health through the application of good scientific methods and research; and
2. The preservation and promotion of respect for persons by the application of good ethical principles and practices in medical research.

Based on a synthesis of various ethical codes, guidelines and literature, a systematic framework of principles designed to be applicable to all clinical research is proposed here.[1] The framework (or set of factors) that determines the ethicality of a clinical research is as follows:

1. **Value,** based on the ability of the study to contribute to a generalisable pool of knowledge in clinical Medicine, and the value of its application for improvements in health and clinical outcomes.
2. **Scientific validity,** based on the methodological rigour that is employed in the study.
3. **Fair subject selection,** based on scientific objectivity with equitable access and selection.
4. **Favourable risk-benefit ratio,** with minimal risk to participants and maximum benefit for individuals and society.
5. **Independent review,** to review the compliance to research ethics guidelines in the design, conduct, audit, analysis and publication of research results.
6. **Informed consent,** to enhance the autonomy of study subjects. It is important to avoid therapeutic misconception, and special measures must be taken when obtaining consent from individuals lacking capacity.
7. **Respect for enrolled participants,** including preservation of medical confidentiality, privacy and the option to withdraw from the study at any stage. The welfare and interest of participants should be upheld uppermost for the study.

Value and scientific validity

A study should be shown to have scientific and social value before it commences. In order to achieve this, the investigator should have clear goals, understanding of the expected results, and how it could contribute to the improvement of healthcare.

Next, good study design helps to attain validity. Poorly designed research would lead to studies with inadequate power, insufficient or sloppy data, or inappropriate or unfeasible methods – all of which would compromise the scientific validity and value of the study.

Conflicts of interest in clinical research

The preservation of scientific validity and integrity is often challenged by conflicts of interest, which is often defined as "a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest".[2] However, stating that someone has a conflict of interest does not imply that the person has been unethical or corrupt.

The primary interest of researchers is to preserve the integrity of medical research and knowledge. Their secondary interests could include personal academic advancement, financial gain for the individual or the organisation, or the promotion of organisational reputation. In such cases, the primary and second interests could come into conflict with each other.

Conflicts of interest are problematic because they risk the integrity and validity of research and science being sidelined by a secondary interest, the integrity of medical judgement being violated, and research and scientific outcomes being compromised. Ensuring the welfare of research participants is an ethical interest that often competes with research interests, rather than a conflict of interest.

Conflicts of interests are ubiquitous in medical research and practice. They have to be managed effectively to preserve the validity of the study and trust in the research community.

Fair subject selection

The Belmont Report states that "there be fair procedures and outcomes in the selection of research subjects" so as to prevent exploitation of vulnerable individuals and populations.[3] A fair subject recruitment process includes clear and specific inclusion and exclusion criteria, as well as an appropriately rigorous consent process for the potential study subjects.

Extra safeguards must be put in place during the selection process, to protect vulnerable subjects who often lack full voluntariness and capacity to provide informed consent.[4] The consent process should include measures to enhance the autonomy of subjects at all times.

Favourable risk-benefit ratio

Clinical research involves exercising aspects of clinical Medicine where knowledge is limited and uncertain. Therefore, clinical research involving human subjects can only be ethical if the study is designed to minimise risks and burdens to the research subjects,[4] and hence achieve a favourable risk-benefit ratio.

The latest amendment of the Declaration of Helsinki in October last year suggests that a favourable risk-benefit ratio can be achieved through careful assessment of predictable risks and burdens to the individuals and groups involved in the research, in comparison with foreseeable benefits to them and to others affected by the condition under investigation.[4]

Independent review

Ethical research must be subjected to review by a truly independent and competent institutional review board, to manage the conflicts of interest and to conduct a comprehensive review to objectively evaluate the study for its compliance to established guidelines.

This review process has been said to be central to the protection of scientific value, validity and research subjects. Besides specifically auditing for exploitation of study subjects, the review process also ensures an objectively favourable risk-benefit ratio.

Informed consent

Before subjects are recruited, they need to provide their informed consent, which allows them to be able to make autonomous decisions about participating and remaining in the research study.

The process of informed consent involves three main elements: information, capacity and voluntariness. Research subjects must be accurately informed about the study's purpose, methods, risks, benefits, and alternatives to it. This delivery of information has to be balanced and presented in a manner that the subjects can fully understand, taking into account their primary language, education levels, and familiarity with research and cultural values.

During the informed consent process, it is important for investigators to be aware of the presence of therapeutic misconception, which is the failure of some study subjects to understand the differences between normal therapy and clinical research. These subjects often express incorrect beliefs and overestimate the degree in which the research treatment will meet their specific needs and the likelihood of benefiting from participation in the study.[5] In addition, they might also misunderstand the investigators' aims in performing the project.

Proxy decision-makers may be employed to help make decisions in special circumstances, such as the enrolment of children and minors where they may be unable or not mature enough to make their own decisions. In making this decision, the proxy must be shown to act in the best interest of the child. Under the Mental Capacity Act, a donee with a lasting power of attorney does not automatically have the right to enrol the patient for clinical research.[6]

Respect for enrolled persons

Respect for research participants requires ethical considerations beyond just signing the consent form and enrolling into the study. Research subjects should be treated with respect throughout the study with careful clinical monitoring, and respect for their wishes and care for their welfare. Participants should be updated on the progress of the study and their health. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.[4] In addition, their private data need to be handled confidentially as well.

To enhance autonomy, subjects should be reminded of their right to withdraw from the study at any time without penalty. New knowledge that emerges during the study or any other related studies should be shared with the subjects if it is likely to impact their willingness to participate.

Conclusion

Strict adherence to research ethics and processes, sometimes known as ethical imperialism, may impede potentially beneficial research or make it impractical to protect research subjects, which could both be detrimental to the promotion of clinical research. However, excessive tolerance to local cultural beliefs and practices may compromise ethical principles, resulting in ethical relativism, which could lead to loss of integrity in the research and exploitation of vulnerable population. A balance can be achieved if the research is guided by ethical principles, good ethical analysis, reasoning and judgement, rather than enslavement to the rules of the book. SMA

References

1. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000; 283(20): 2701-11. Available at: http://jama.jamanetwork.com/article.aspx?articleid=192740. Accessed 30 December 2013.
2. Lo B and Field MJ, eds. Conflict of interest in medical research, education, and practice. Available at: http://goo.gl/AZztyV. Accessed 30 December 2013.
3. The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Washington DC: US Government Printing Office, 1978. Available at: http://www.hhs.gov/ohrp/policy/belmont.html. Accessed 30 December 2013.
4. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3. Accessed 30 December 2013.
5. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. IRB 2004; 26(2): 1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15069970. Accessed 30 December 2013.
6. Attorney-General's Chambers. Mental Capacity Act (Chapter 177A), Section 22(1)(d). Available at: http://goo.gl/DdWxZT. Accessed 30 December 2013.

Shunjie is a third year MD student at Duke-NUS Graduate Medical School. Before medical school, he was an engineer trained in Japan. He has a lifelong goal of becoming a clinician scientist.

Dr Thirumoorthy holds the position of Associate Professor in the Education Programme, at the Duke-NUS Graduate Medical School, Singapore, since 2007. His teaching responsibilities include subjects on professionalism, medical ethics, communications, and healthcare law.