Commentary

Ethical Issues in Ophthalmology and Vision Research

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Abstract

As more research work is done on eye disorders, more safety rules and regulations are required to ensure the safety of trial subjects. This is the main function of Research Ethics Committees [also known as Institutional Review Boards (IRBs) and Domain Specific Review Boards (DSRBs)]. Tragedies in research in other fields are wake-up calls, such as the death of a healthy young volunteer subject in New York, the termination of a large study sparked by breach of medical confidentiality in Singapore and the South Korean debacle of its pioneering work in cloning. Many issues are still being debated, such as what statutory changes are required to control trials; whether all trials should be reviewed by IRB; if phase IV trials should be exempted; if compensation should be paid for all trial-related injuries; and whether investigators and IRB members be allowed to hold certain amount of shares in drug or device firms. Recent measures taken to prevent ethical problems include funding organisations not approving a study unless it has been cleared by the IRB, and requiring all investigators and IRB members to pass an ethics course. More measures will need to be taken to ensure the safety of the trial subjects involved in research studies.

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Introduction

The importance of ethics in research was highlighted in the USA when a healthy volunteer subject, 24-year-old Ellen Roche, died in a Johns Hopkins asthma study in 2002. Investigations showed that there had been serious deficiencies in the ethical review and research work was suspended in Johns Hopkins until recommendations by the Office for Human Research Protection were implemented. In Singapore, we got a wake-up call in 2003 when a large study, carried out at the National Neuroscience Institute on patients with Parkinson's disease, resulted in complaints of breach of medical confidentiality and protocol deviations. The withdrawal of drugs, such as Baycol in 2002, Vioxx and Celebrex in 2004, Tysabri and Bextra in 2005, from the market because of fatalities showed that a drug may still not be safe even after years of trials and testing. Worse still was the revelation that some drug manufacturers had suppressed data events. Worst of all is the case of South Korea's cloning pioneer, who had faked his research results. All these recent events have highlighted the importance of the ethical review of clinical trials.

History

Background knowledge of the history of Research Ethics Committees [also known as Institutional Review Boards (IRBs) or Domain Specific Review Boards (DSRBs)] in Singapore is important in understanding why we are encountering some of the problems we have.

On 18 June 1995, the National Medical Ethics Committee (NMEC) was founded. Two years later, on 4 September 1997, NMEC published its "Ethical Guidelines on Research involving Human Subjects".[1] This was patterned after guidelines set up by the World Health Organization (WHO), the Royal College of Physicians (RCP, London)[2] and the Medical Research Council (MRC, Canada). On 25 June 1998, the Ministry of Health (MOH) circulated a paper[3] to its health care institutions recommending that the hospital ethics committees vet all research protocols. At the same time, on 1 July 1998, the Singapore Guideline for Good Clinical Practice (SGGCP)[4] together with the amalgamated version of the Medicines (Clinical Trial) Regulations Act 1978 and 1998 (MRA)[5] were officially launched. Since 1996, the SGGCP has been incorporated by reference in

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Regulation 21 of the MRA. Sponsors and researchers in pharmaceutical trials are required by law to comply with the SGGC unless specifically exempted under the Medicines (Clinical Trial) Regulations. The SGGCP and MRA are based on the guidelines set by the International Conference on Harmonization (ICH), governing only drug trials. By law, "clinical trials" are defined as drug trials only.

On 28 August 1998, the MOH circulated another paper[6] which stated that "Non-drug clinical trials for medical devices and medical procedures do not fall under the purview of the Medicines Act... However, the MOH is of the view that the SGGCP is a desirable standard for all Clinical Trials..."

The current Medicines (Clinical Trial) Regulations Act is the 2000 revised edition. Other guidelines, which are non-statutory, have been formulated by the NMEC and the Bioethics Advisory Committee (BAC).

Types of Trials

There are therefore many trials which are not governed by our statutory regulations [the SGGCP and the Amalgamated version of the Medicines (Clinical Trial) Regulations 1978 and 1998]. By these laws, clinical trials refer only to drug trials. Table 1 shows a list of the types of research trials.

Table 1. Types of Trials

• Clinical trials	Drug Trials governed by SGGCP and Medicines (Clinical Trial) Regulations
• Trials on	
Medical devices	CMDR (Centre for Med. Device Regulation)
Animal studies	IACUC (Animal Care and Use Committee)
• Genetic research	NMEC Guidelines on Gene Technology
• Embryonic stem cell research and cloning	BAC (Bioethics Advisory Committee) Guidelines on Human Embryonic Stem Cells and Human Cloning
• Human tissues	
Living donors	BAC Guidelines (including fetuses and fetal tissue)
Cadavers	Medical (Therapy, Education and Research) Act and HOTA (Human Organ Transplant Act)
• Epidemiological studies	
• Retrospective studies	
• Medical procedures studies	
• Observational clinical trials	
• Health supplements trials	
• Complementary medicine trials	
• Approved (Registered) drugs trials	
Off-label indication	
New dosage/new route of administration	
Drug vs standard treatment	
Drug vs placebo	

Are Statutory Changes Required?

Can our present statutory regulations[4,5] be amended to cover all research studies? Can we simply redefine "clinical trials" as meaning all research studies and not only drug trials? If we do this, many amendments will need to be made. For example, under the Medicines Act and the Medicines (Clinical Trial) Regulation, the Principal Investigator (PI) or Supervisor of a trial must be a doctor/dentist. This will need to be amended to allow for non-medical persons to conduct trials. It would be easier to have new regulations for clinical research, which address all types of clinical research.

Can Non-physicians Do Eye Research?

IRBs are increasingly being asked to review research studies done by non-physicians. As long as "drugs" are not involved, by law, it is permissible for non-medical personnel to carry out such studies. However, non-physicians do not have medical protection insurance for defence and compensation in the event they are sued by a trial subject. Institutions which support non-physicians doing research work should have insurance policies covering such research.

Medical Confidentiality

It is understandable that patients would not want others to know that they have eye disease or are going blind. We should therefore be careful not to breach medical confidentiality. It is not appropriate to recruit subjects for trials from the Medical Records Department, Radiology Department, Pharmacy or Laboratory, without informing the attending physician. We do not want to be asked by the subject, "How do you know that I have glaucoma?" It is also prudent to ask the attending physician for permission to approach his patient, in case one is accused of touting for patients, in the name of research. However, for trials where recruitment through the attending physicians is slow, researchers can resort to advertisements in the media, posters in the clinic, brochures, etc. Of course, all these need prior ethics review and approval. The SGGCP states in Section 4.3.3. that "it is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed."

Conflict of Interest

With IRB Members

An IRB member with a conflict of interest cannot participate in the initial or continuing review, except to provide information requested by the IRB. The IRB member concerned will have no voting rights. Some IRBs require

that he or she leave the meeting room during the final deliberation and voting.

It is important to make sure that there will still be a quorum present if there are IRB members who have conflicts of interest.

With Investigators

Some examples of conflict of interest are:

a) A head of department approving a study of which he is an investigator.

b) An investigator of a trial study:
   - Serving in the board of directors of a company whose product is the subject of the trial study.
   - Holding shares in the manufacturing company or drug firm.
   - Receiving excessive remuneration for the trial study.
   - Receiving royalties or future royalties from the commercialisation of the research result or products, including entitlement to any "milestone" payments conditional upon specified research-related dates or events.
   - Receiving income for consulting, advisory or lecturing services from the firm.
   - Having material ties with the journal that publishes the results of the research.
   - Having immediate family members (e.g., parents, siblings or children) who have financial interests that may present the appearance of a conflict of interest. These interests, except diversified financial holdings, such as mutual funds or unit trusts, should be disclosed.
   - The department or institution receiving royalties from the sale of the research product.

The Centre for Science in the Public Interest, an advocacy group in Washington, reviewed articles published in 4 medical journals, and found a dozen studies, published in 2004, in which researchers had failed to disclose financial conflicts of interest.[7]

Should We Set Limits on Financial Involvement?

Some countries allow for a limited financial involvement, e.g., holding shares in the drug firm up to the value of USD30,000. How about unit trusts or mutual funds? Will investigators or IRB members be allowed to own such funds which invest in the drug firm? Or is this permissible as long as they disclose their financial interests?

Should the Principal Investigators be Conducting the Consent Process?

The PI wants to recruit subjects for his study as quickly as possible, and he is therefore biased. It is likely that he is also the subject's physician, in which case the subject becomes vulnerable because he or she would probably not want to offend the physician in case his or her treatment was affected. Should the PI then be conducting the consent process?

Who are Vulnerable Subjects?

Some subjects are particularly "vulnerable" because of pressures from the investigator or institution, critical illness, mental incapacity or immaturity. They include children, mentally ill patients, prisoners, employees and students. Special precautions need to be taken in obtaining their consent.

Are Incentives Permissible?

It is permissible to reimburse subjects a reasonable amount for transportation, such as $25 per trip. To give the subject more may be seen as giving them an inducement to participate. Rewards and incentives, such as vouchers, should have approval from the IRB before they are given.

Adverse Events in Eye Research

Very often, mydriatics/cycloplegics are used in eye research studies. It is well known that these eye-drops cause blurring of vision, and this side effect should be emphasised in the subject information notes. Subjects should be reminded of the consequences of blurred vision, such as slipping, falling down, and clumsiness. Children and the elderly should be accompanied, as they are more prone to such accidents. They should be supplied with sunglasses if glare is a problem, or multifocal or progressive glasses for near work.

It is also well-known that such drops can precipitate angle-closure glaucoma. This is not uncommon. This side effect should be emphasised in the subject information notes.

Special care should be taken whenever steroids are used in the eye as they can cause cataracts, glaucoma, infection and dendritic corneal ulcers.

Who Should Compensate for Trial-related Injuries?

This is dealt with in the NMEC Guidelines[1] 3.3.2, the SGGCP[3] 4.3.2. and the Medicines (Clinical Trial) Regulations[4] 5.3.

The sponsor is liable for compensation, as spelt out in SGGCP[3] 5.8.1 and NMEC Guidelines[1] 3.3.2. However, in the event that the investigator is proven negligent, his medical protection insurance is liable. In industry-initiated trials, the sponsor is the company. Most companies adopt the Guidelines of the Association of the British Pharmaceutical Industries (ABPI), a copy of which should be made available or given to the subject. In investigator-initiated trials, the institution is the sponsor, and should

compensate the subject for any trial-related injury. As with ABPI guidelines, only unexpected (not listed in the subject information notes) adverse events are covered. No compensation is paid in respect of adverse events that have been set out in the subject information notes and are expected. In all cases, emergency medical treatment should be available.

Genetic Studies

An increasing number of studies for review involve genes. Table 2 shows some of the special features to emphasise, as found in NMEC's "Ethical Guidelines for Gene Technology."[8] For example, because DNA information can affect the subject's employability, insurability and reputation, special attention to medical confidentiality is required. All samples and information should be double-coded, with one code for the patient database, and another code for the genetic database. Protective measures should be in place to restrict access to the site where the codes linking patient-identifiable information to the genetic database are maintained.

Review of Clinical Trials

Those who are not familiar with the IRB/DSRB are not aware of the voluminous amount of work related to the review of a clinical trial. Table 3 gives an overview of the documents that are reviewed for every trial.

How Many Protocols Should an IRB Review?

As most IRB members are busy professionals, it would be trying for a member to review more than 10 new applications a month. It would also be trying for an IRB meeting to deliberate on more than 10 trials in one evening. IRBs not only review new applications but continue overseeing research study until the end of the study by reviewing protocol amendments, serious adverse event reports and annual reports.

The Application Form

Should an IRB accept the application form of a funding organisation as an application for IRB review? As funding organisations look mainly at the scientific aspect of a study, and not at the ethical aspect, an IRB should have its own application form; e.g., in the ethical review, the recruitment methodology is important from the point of view of medical confidentiality and patient privacy.

How to Start Reviewing a Clinical Trial

Faced with numerous voluminous files, how does an IRB member begin to review them? A good place to start is the subject information notes, which explain, in layman's language, what the study is all about. If I do not understand any word or sentence, I ask that it be further explained in layman's language. The thickest file is usually the investigator's brochure, which lists all the past animal and human studies and their results. Its review can be assigned to a scientific panel, or a Primary Reviewer and Secondary Reviewer in the IRB.

Table 2. Gene Studies

• Specify duration of storage of blood
• Specify identity of the gene
• State "used only for the purpose of this study"
• Subject can request his sample to be destroyed
• Maximal confidentiality (double-coding)
• Explain risk to subject's employability, insurability and reputation if misused
• Explain that commercialisation of the results will not benefit him

Table 3. List of Documents for IRB Review

Application form
Trial protocol
Informed consent with subject information notes
Investigator's brochure, with lists of previous animal and human studies, known risks and complication rates
Subject recruitment procedure, with any advertisements, posters, etc.
Principal investigator's curriculum vitae
Financial statements, with details of payments, compensation, sponsorship, indemnity, etc.
Continuing review of adverse events
Progress reports with results
Completion reports

Should IRB Have a Scientific Panel?

If a study is scientifically or methodologically flawed, it is unethical to carry it out. Scientific approval of a study is therefore very important. For example, is there sufficient statistical power in the study? Some IRBs rely on scientific panels which examine the study from a scientific point of view. Other IRBs consult specialists whenever required. Funding organisations usually approve studies on their scientific merit. Should IRB accept the findings of the funding organisation and not do another scientific review? Most funding organisations give only conditional approval until ethical clearance by an IRB. The BAC guidelines recommend that the IRB is responsible for ensuring that the scientific review was adequate.

Which Reviews May Be Expedited?

A review may be expedited and not require a formal IRB meeting. Such a protocol can be reviewed by the chairman or his nominee, or be circulated to IRB members for comments. The following protocols may be expedited:

a) Minor changes in a previously approved study (SGGCP 4.5.2).[3]
b) Study approved by another IRB (NMEC Guidelines 3.3.5.3).[1]
c) Study with not more than minimal risk.

Which Studies may be Exempted from IRB Review?

The IRB Chairman may decide that some trials be exempted from review. Such trials include:

a) *Retrospective studies*
Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

b) *Prospective studies*
Research involving educational tests (cognitive, diagnostic, aptitude, achievement), or observations of public behaviour, unless:
   i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
   ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation.

It would be prudent to keep IRB members informed of those studies which have been expedited or exempted from review.

In Which Studies May Consent Be Waived?

Consent may be waived in some studies involving the following:

a) Emergency (SGGCP 4.8.15 ; Med. Reg. 1998, 11A[3]; GMC Guidelines on Research 51-54).
b) Epidemiological survey that cannot be done without a waiver of consent.
c) Retrospective (records-based) study that cannot be done without a waiver of consent.

Conclusion

The importance of ethics in research is now acknowledged. The MOH has recommended that all research studies be reviewed and approved by the IRB. Funding organisations will not approve a study unless it has been cleared by the IRB. All investigators and IRB members are now expected to pass a self-assessment course on ethics. All these measures are taken to ensure the safety of the trial subjects involved in research studies.

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