Research Ethics, Governance, Oversight And Public Interest

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Abstract: A better educated public has started to challenge the way decisions are made in medical research activities. Although Institutional and National Guidelines on Research are in place, there are fears that Institutional Review Boards (IRBs) and funding agencies are only fairly active in scientific and ethical reviews of research proposals but not on oversight of projects after their initiation. These issues are integral to good research governance and researchers and custodians of research ethics must ensure that public interest is not compromised.

Medical progress is based on research including human experimentation carried out according to guiding principles as enunciated in the Declaration of Helsinki (2000), but the quality of compliance with the Declaration is an important issue.

Better choice and appropriate training of members of IRBs to improve the quality of decision making and governance processes are urgently needed. Competency in evaluation of proposals requires not only the appropriate scientific knowledge but also access to relevant preclinical and other data. Unfortunately, the completeness and quality of such data may not be adequate.

Public interest demands that injury to trial subjects in clinical trials is minimized if not avoided completely. Unfortunately this is not always possible with trials where novel biological modes of action are tested. A more robust evaluation mechanism for project approval may minimize but not completely avoid injury to subjects; thus insurance cover to provide care and compensation to subjects must be compulsory.

The decision to approve or reject a project must be based on the balance of potential risks and benefits, taking into consideration justifiable distributive risks to target communities and populations. Economic considerations should never be the primary focus, especially when there are real concerns that the migration of early phase clinical trials including vaccine trials to developing countries is based on the perceived less stringent ethical requirements and oversight there.

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Introduction

There is no doubt that the practice of medicine is shaped by advances in basic, applied and translational research. Research activities have and will continue to impact on the lives of health professionals, researchers and the public. It is recognised that research must be needed, ethical, safe, and must be conducted professionally. But who are the custodians of these values associated with medical research? And are those tasked with these duties sufficiently trained?

A better educated public with internet access to information has started to challenge the way decisions are made in areas where their health are directly or indirectly affected, including medical research activities. Public discontent and outcry against perceived unnecessary, unethical, or scientifically flawed studies are just beginning in Malaysia. The move by multinational pharmaceutical companies to migrate early clinical trials to developing countries has also generated various concerns. Inadequate, inappropriate, and premature release of information on planned field research activities have also caused undue fears in the public.

Most if not all major Institutions with medically related research activities have their own Institutional Review Boards (IRBs) charged with responsibilities to ensure that national and international guidelines[1-3] on human experimentation are followed. Although Institutional and National Guidelines on Research are in place, there are fears that IRBs and funding agencies are only fairly active in scientific and ethical reviews of research proposals but not on oversight of projects after their initiation. Neither is there confidence that the whole process from project approval, monitoring, reporting including publication, scientific communication, etc, and evaluation of the 'utility' of results, is sufficiently robust. These issues are integral to good research governance and researchers and custodians of research ethics must ensure that public interest is not compromised.

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Research Ethics

Medical progress is based on research including human experimentation, but the well-being of the subject is paramount. While all medical research involving human volunteers must conform to the principles as enunciated in the Declaration of Helsinki[2], some researchers and even regulatory agencies including those in developed countries, may not follow some of its provisions or worse still, use loop holes in the latest revisions. Thus compliance and the quality of such compliance with the Declaration are important issues. The Declaration which is in its 5th revision, is considered a living document[4] and regular revisions have been made to accommodate changing societal mores, ethical standards, and scientific advances. The global community must ensure that any revision should not compromise the fundamental principles of volunteer safety and welfare, integrity, informed consent, and best practice approach. A recent concern is that the FDA may not follow the Declaration of Helsinki with regard to mandated comparison with the best practice or therapy in clinical trials[5].

There are concerns that the quality of decision making in IRBs vary within and between nations. There are calls for the reforming of research ethics committees[6] as some are perceived to be slow, idiosyncratic, poorly informed about research methods or guidelines on research ethics. Better choice and balance in membership to reflect expertise is needed and appropriate training of members of IRBs can improve the quality of decision making and governance processes. Expertise not available among members may require sourcing externally, if issues of confidentiality are appropriately ensured. This is so as ethical review may require alteration of the scientific approach of the study, and this forms part of research governance.

Research Governance and Oversight

An often neglected area in biomedical research but less obvious in multi-centre clinical studies, is the monitoring of research project activities after approval. Although data and progress reports are required and collected regularly, good research governance requires timely analysis, interpretation, and appropriate action. More importantly, monitoring of research projects includes ensuring subjects are protected at all times and that there is no unauthorised deviation of the agreed research protocol.

Spectacular advances in basic research have opened the potential and promise of new therapies and other applications in medical fields, a very good example being stem-cell based therapy. Yet there is difficulty in defining the line between research and therapy[7], with the knowledge that there will always be risks involved when research is translated to clinical application. Adverse reactions are mainly of two types, those unrelated to its intended action like liver toxicity and leucopaenia, and those related to its intended biological target as in the TGN1412 humanized monoclonal antibody incident[8]. In this instance, six trial subjects developed near fatal multi-organ failure that required prolonged hospitalization. Death can and has occurred in clinical trials as seen in the unfortunate death of an 18-year old patient with an ornithine transcarbamylase deficiency following adenoviral gene transfer and who developed fatal systemic inflammatory response syndrome[9]. Although risks can be minimised by not treating multiple volunteers simultaneously and having a longer interval between test subjects to monitor early and late effects, a Phase I clinical trial is essentially a journey into the unknown[8].

The above recent, well-publicised severe adverse reactions seen in clinical trial subjects have raised questions as to whether oversight by IRBs has been adequate. Competency in evaluation of proposals requires not only the appropriate scientific knowledge of the members but also access to relevant preclinical and other data. The decision as to whether a particular compound, device or procedure is ready for clinical trials is sometimes made based on the premise that all laboratory, animal, and preclinical data are sufficient and have been presented. Unfortunately, the completeness and quality of such data may not be adequate and there may be pressure to approve a project. The database of competitors in drug development,

for example, may not be available to the IRB when a request for the study compound is submitted for approval. Recommendations for a secure database available to members of the IRB have been suggested as a mechanism to overcome this problem.

The use of animals for preclinical studies can contribute vital information on possible adverse or toxic effects of new therapeutic or bioactive compounds. It is now realised that evaluation of these entities in non-human primates is essential and there is urgent need for appropriate non-human primate experimentation[10].

Field intervention studies are often not given the scrutiny in the approval process as clinical trials are and yet the potential for harm to the environment and population can be disastrous. Vaccine field trials and release of genetically modified organisms for disease control or economic reasons need as much if not more stringent evaluations and oversight.

A growing concern by those tasked with research governance is prevention and detection of fraud. While it is recognised that preventive measures through appropriate training at the undergraduate and graduate levels can have a positive impact, the temptation to plagiarise given the ease of access to primary sources of data in the internet is indeed great. The drive to produce results at all costs have let to incidences of fraud like the Korean cloning scandal, with disastrous consequences and issues of accountability[11] to the researcher, institution and country.

Research and Public Interest

The whole process from project approval and final utilisation of research results is integral to good research governance. Public interest demands that injury to trial subjects in clinical trials is minimized if not avoided completely. Unfortunately this was not possible with trials where novel biological modes of action are tested as seen in the unfortunate incidents with adenoviral gene transfer and humanized monoclonal antibody studies. A more robust evaluation mechanism for project approval may minimize but not completely eliminate injury to trial subjects; thus insurance cover to provide care and compensation to subjects must be compulsory. Another situation which could potentially cause injury to a greater number of individuals would be field studies involving premature release of genetically modified organisms into the environment for disease control. Thus the potential use of genetically modified Aedes aegypti mosquitoes to control dengue[12] must be thoroughly evaluated before implementation to avoid potential population-based disasters.

Law suits by injured subjects in clinical studies against investigators, IRBs, and academic institutions are increasing and this trend will have an impact on their functions[13]. However, compensation for injured subjects is extremely variable even in developed countries. US sponsors and institutions unlike those in European countries are not required to provide either free medical care or compensation[14].

The decision to approve or reject a project must be based on the balance of potential risks and benefits, taking into consideration justifiable distributive risks to target communities and populations. Economic considerations should never be the primary focus, especially when there are real concerns that the migration of early phase clinical trials including vaccine trials to developing countries is based on the perceived less stringent ethical requirements and oversight there.

Other peripheral issues which affect the public are those concerned with premature termination of multinational clinical trials. Issues related to this are whether centres and IRBs have available data and authority to make appropriate decisions. Will such premature termination impact on the quality of the results and thus any subsequent decision based on them? Another current topic will be subject benefit and financial rewards arising from commercialisation of research findings based on subject samples and tissues[15]. Central to all this is the question, 'Who looks after subjects' interest?' Do subjects sign away all rights to this when they are properly recruited and have agreed to volunteer after giving 'informed consent'?

Conclusion

IRBs are expected to consider a list of important issues whenever they evaluate a research proposal for scientific and ethical appropriateness. In particular, these include, scientific need and soundness, subject safety, confidentiality and integrity, and the quality of informed consent. Other issues to be considered include balancing between public good and public interest, public safety and public risks, equitable distribution of risks, and protection of vulnerable groups.

Ethics and the associated regulatory framework are constantly evolving, and the challenge will be to balance these changes to enable them to be in tune with advances in technology and their applications in medicine. We need to have credible, well trained IRB members to provide the leadership and who are prepared to make difficult decisions based on all available facts.

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