MEMORIAL LECTURE OF
PROF. C.SIVAGNANASUNDRAM
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HOW SHOULD WE DO RESEARCH?

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Professor Chellathurai Sivagnanasundram Memorial Lecture - 2015

Vice- Chancellor's Message

We are proud to have Prof.Arunasalam Pathmeswaran, Professor in Public Health, University of Kelaniya to deliver Prof.C.Sivagnanasundram Memorial Oration 2015.

Prof.Pathmeswaran is a well known academic as a Professor in Public Health as well as in biostatistics. He teaches biostatistics, epidemiology, research methodology and public health to both Undergraduates and Postgraduates in Health Sciences including Medicine. We are fortunate to have Prof.Pathmeswaran because both Prof.Sivagnanasundram and he had common interest in the subject specialities. Furthermore the topic selected by Prof.Pathmeswaran is well suited for the interest of Prof. Sivagnanasundram where Prof.Sivagnanasundram has published a text book for the beginners of research, titled 'Learning Research'.

I thank Prof.Pathmeswaran for agreeing to deliver Prof.C.Sivagnanasundram Memorial Oration 2015 on the title 'How should we do research?'. I believe this would be a suitable topic for those who are the beginners and those who want to strength their research activities

Prof.(Ms.)V.Arasaratnam
Vice-Chancellor
University of Jaffna

How should we do research?

Professor C. Sivagnanasundram Memorial Lecture- 2015

Vice chancellor, staff and students of the University of Jaffna, members of the family of Prof. Sivagnanasundram, ladies and gentlemen – I am honored and humbled by the invitation to deliver the Prof. Sivagnanasundram memorial lecture this year. I wasn't fortunate enough to have been taught by Prof Sivagnanasundram or to have even met him. But I feel connected to him as I have interacted with some of his colleagues like Dr Sivarajah and late Prof Malcolm Fernando; I know very well two of his students - Prof Sivayogan who was my teacher during my postgraduate days and now a good friend and Dr Surenthirakumaran who started as one of my postgraduate students and now a good friend. Based on the recollections of these people I feel that I know a little about Prof Sivagnanasundram.

Learning Research or Learning how to do research

Research is essential for progress in any academic discipline. The need for and the importance of research is appreciated by both the academic community and the wider community. As with any good tool research can also cause harm if not done 'correctly'. This will lead to loss of public confidence and

may even lead to hostility towards research and researchers. Recognizing the importance of the need to do research and the lack of a suitable book for budding biomedical researchers in our country Prof Sivagnanasundram authored and published the book 'Learning Research' in 1999. Even though I know very well that Prof Sivagnanasundram had varied interests and excelled in many fields for me he is simply the man who wrote 'Learning Research'. This book deals with every aspect relevant to doing a research project. From the identification of a research problem, developing the methods, executing the project, analyzing the data and communicating the findings.

Premedication for antivenom trial

In 2005 one of the patients who participated in a clinical trial I was involved in died. How do I feel about this incident? Should I feel guilty about this death?

Envenoming following snakebite can kill the victims and the antivenom used in our country as the antidote can also kill. In fact about 200 Sri Lankans die every year following snakebite. We do have guidelines for the use of antivenom but we do not have any guidelines for the prevention or treatment of reactions to antivenom. Adrenaline, antihistamines and corticosteroids were the commonly used drugs in the prevention and treatment of reactions to antivenom

We designed a factorial trial to test the efficacy of the three drugs -low-dose adrenaline, promethazine, and hydrocortisone alone or in combination as premedication to prevent reactions to antivenom following snake bite (de Silva et al., 2011).

This was not the first death in the trial but the first at that particular hospital. We had considered the possibility of harm to the patients taking part in the trial and built in several mechanisms to minimize the likelihood of the trial causing harm. We had arranged close monitoring of patients, established a data safety monitoring committee and planned for several interim analyses, obtained informed consent from the patient or responsible relative and obtained approval from an ethical review committee. The trial protocol also allowed the treating physicians total freedom to manage individual patients appropriately. In spite of all these precautions 13 out 1007 trial participants died. Therefore I don't feel guilty about these deaths.

How should we do research?

It is not only the technical aspects of designing and implementing research that are important but the ethical conduct of research and researchers are also very important. The simple answer to the question – How should we do research? – is that 'we should do research without violating the rights of others'. We should not violate the rights of research participants, fellow researchers and the public.

Research ethics the traditional approach

It is the last section of the methodology in the research proposal. Ethics is the title of chapter number 20 in Prof. Sivagnanasundram's book. For many researchers ethics is a matter of checking or ticking boxes by the applicant and reviewers.

Introductory workshops on research ethics deal with four principles; or sometimes with three principles. The four principles are autonomy, nonmaleficence, beneficence and justice, but nonmaleficence & beneficence can be taken together as these are considered as two ends of a spectrum.

Problem with the principle of nonmaleficence / beneficence is that this implies an unequal relationship between the researcher and the research subject. In instances where the researcher is a clinician and the subjects are patients under their care there is an unequal or paternalistic relationship and most ethical guidelines address this issue.

Historical developments

Hippocratic Oath (~400 BC)

The Hippocratic Oath is about the behavior of medical practitioners as practitioners and not as researchers (Markel, 2004). The oath being more than 2000 years old is often misquoted. For example the phrase "First, do no harm" is not actually in the oath, but it was mentioned by Hippocrates in another document. The oath mainly deals with the physician's relationship with his or her teachers, fellow physicians and patients. Due to the universal appeal of this oath almost all codes and declarations on ethics of biomedical research quote this. There are some incompatibilities between the role of a physician and the role of a researcher. The physician's primary concern is the treatment of individual patients whereas the researcher's primary concern is finding the truth. Therefore it is important to take these into consideration when using the Hippocratic Oath as a resource material for developing codes of conduct for biomedical researchers.

Nuremberg code (1947)

Probably the first comprehensive formal document dealing with medical research is the Nuremberg code developed in 1947 by the War crimes tribunal at Nuremberg (Shuster, 1997). Protecting the research subjects can be considered as the main feature of the Nuremberg code. It should be remembered that the code came into existence to facilitate the trial of the German physicians who had been involved in large scale experiments on humans. Many of the German physicians and researchers had shown almost total disregard for the welfare of the research subjects who were either prisoners or concentration camp inmates.

There are several issues that make me uncomfortable with the Nuremberg code.It has a negative focus. It is more on prohibiting bad practices than about promoting good practices. The purpose of the code was to help the American prosecutors to prove the case against the accused Nazi doctors. This code came into existence as a formal document only after the events had taken place. If the contents of the code were made into law it would have been termed retroactive legislation (ex post facto). I think use of such laws in prosecutions is prohibited in the US constitution.

Universal declaration of human rights (1948)

This was proclaimed by the UN general assembly in 1948(UN, 1948). Almost all of these rights had been accepted by many countries previously but the atrocities committed by the Nazi's during the Second World War made the member countries of the

UN to work on such a declaration. Though what comes to our mind when we think of the declaration of human rights are civil and political rights there is enough in this declaration to ensure that research involving human participants is conducted properly if the rights of the participants are recognized and protected by the researchers.

Declaration of Helsinki (1964 to the 7th revision in 2013)

The original Helsinki declaration was just a one page document (Williams, 2008). Being a document produced by the World Medical Association its main aim was to give guidance to doctors involved in clinical research. The declaration gives guidance on fulfilling the dual roles of physician and researcher. The physician researcher is faced with some conflicts in fulfilling his / her responsibilities as the personal physician of an individual patient trying to maximize the wellbeing of the patient while playing the role of an unbiased researcher. The main reason for this conflict is the incompatibility between the paternalistic doctor patient relationship and the concept of autonomy of research subjects. As a physician you want to ensure the best possible treatment and outcome for your patient and you are not too concerned about making decisions on behalf of the patient. In contrast, as a researcher you are expected to provide all relevant information to the research subject and let the subject make the decisions.

The impossibility of dealing with this conflict is reflected in the increasing length of the revisions of the declaration of Helsinki.

Belmont Report (1979)

In spite of the existence of the Nuremberg code and the declaration of Helsinki scandals regarding the conduct of research involving human subjects were reported on and off in the media from many countries including the United States. In 1974 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in the United States. The commission was instrumental in the production of the Belmont Report which elaborated the ethical principles and guidelines for the protection of human subjects of biomedical research (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979).

The Belmont report deals with –

1. Boundaries between practice and research
2. Basic ethical principles
    a. Respect for persons
    b. Beneficence
    c. Justice
3. Applications of these principles
    a. Informed consent
    b. Assessment of risks and benefits
    c. Selection of subjects

There is a reason for the Belmont report to start with the subject of boundaries between practice and research. The Belmont report was in response to the abuse, in many instances

rather subtle, of patients involved in medical research by their own doctors, whereas the Nuremberg code was in response to the gross abuse of prisoners in medical research.

Fetal effects of exposure of pregnant women to organophosphorus compounds study

Organophosphorus compounds based pesticides are often indiscriminately used in agriculture with few safety precautions. Children of pregnant and lactating mothers could be exposed to organophosphorus compounds due to environmental drift or residues in food. This may lead to hitherto unrecognized or undetected adverse health effects. We wanted to investigate the possible impact of chronic, low level exposure of pregnant mothers to organophosphorus compounds on the fetus.

From the 66 pregnant women who participated in the study we collected 2ml of maternal blood and 5ml of cord blood at the time of delivery, and collected 2ml of breast milk within 24 hours post-partum (Samarawickrema et al., 2008).

What does informed consent mean in this situation? How much information should be provided about the purpose of the study? How do we ensure that the participant had understood the information provided?

Problems

1. Research is not always experimental

The main focus of these existing codes is that their primary focus is medical experiments. But biomedical research is much more than experiments. Experiments are where the researchers manipulate external conditions and the subjects are exposed to an external agent for the sake of the experiments. The most common example of a medical experiment is a clinical trial comparing the effectiveness of a new therapy with existing therapy or a placebo. But majority of biomedical research is based on observational design. The Nuremberg code, the declaration of Helsinki and other guidelines are considered as rather restrictive by many epidemiologists conducting observational studies. In 1981 Kenneth Rothman a renowned epidemiologist published a paper in the New England Journal of Medicine titled 'The rise and fall of epidemiology' (Rothman, 1981). In this paper he explains how the guidelines and codes developed to protect the human subjects of experimental research make the conduct of observational studies difficult or impossible. In this paper he relates the story of a researcher who spent one year to get approval from many ERCs to conduct a multi-center observational study.

2. Continued need for monitoring to ensure compliance

As long as there is a power relationship or unequal relationship between the research subjects and researchers the possibility for violations will be there. The researchers may comply with all the codes and guidelines in the legal sense, but not in spirit.

Some of them will always find loopholes in the existing codes and guidelines. This has led to the almost unending spiral of stricter codes and guidelines dealing with the ethical aspects of biomedical research involving human subjects. The original Helsinki declaration made in 1964 was a one page document and the current version has four pages(World Medical Association, 2013).

The ethics review committees (ERC) or the institutional review boards (IRB) as they are called in the United States have been entrusted with the role of ensuring compliance with the relevant codes and guidelines by the researchers conducting research on human subjects. Now there are national and international organizations whose task is to recognize or accredit individual ERCs.

3. Conflict between researchers and ERCs

There is the danger of the ERCs and the review process becoming bureaucratic and the researchers taking the review process as just another administrative hurdle to deal with when doing research. The researchers in their enthusiasm to get on with their research project may forget that the purpose of the review process is to protect the research participants. There is the real danger of discordance between actual conduct of the research project and what is in the protocol.

New researchers or small research teams might find the regulatory process too time consuming and may lose interest in doing research. In order to comply with the regulations and

guidelines very detailed participant information sheets and consent forms have to be prepared and translated into local languages.

The participant information sheet and the informed consent form of international clinical trials run into several pages. I sometimes wonder whether it is really possible for participants without a degree in law to understand these documents fully.

Way forward

Rights based approach to research ethics

All of us are familiar with the idea of rights based approach to health and development. Empowering communities is considered as the best approach to deal with the range of health problems we are faced with today. Rather than depending on researchers to comply with ethical guidelines and the ERCs to ensure compliance we should empower the patients and the public about the ethical issues involved in conducting biomedical research. A well informed public aware of their fundamental rights and a research culture respecting the rights of all is likely to promote ethical conduct of research.

Rather than starting with ethical principles that form the basis of codes and guidelines for ethical conduct of research we could base these codes and guidelines on the universal declaration of human rights. In my opinion nine of the thirty articles in the universal declaration are directly relevant to biomedical research; the others mainly deal with civil and political rights.

For ease of presentation I'll use the Belmont declaration as the point of reference to demonstrate the adequacy of the universal declaration of human rights in dealing with issues related to ethics in biomedical research. The third part of the Belmont report deals with applications of ethical principals in relation to informed consent, assessment of risk benefit and selection of subjects.

Informed consent

Informed consent can be considered as the process by which the principle of respect for persons or autonomy is applied in practice. There are three aspects to informed consent. These are the information to be provided, assessment of comprehension and voluntariness. These are dealt with in the first article of the universal declaration which states that human beings are endowed with reason and conscience. This implies that human beings have the capacity and the right to make decisions on their behalf.Article 12 deals with the right to privacy implying that data related to individuals cannot be used for any purpose for which they have not given permission for. Article 19 guarantees the right to information and article 25 guarantees the right to medical care.

Assessment of risk & benefit

Assessment of risks and benefits is the process by which the principle of justice is applied in practice. Risk benefit analysis deals with the probabilities and magnitudes of possible harms and benefits. This gives rise to the problem of dealing with differences in the probabilities and magnitudes at the same time.

How can we compare a low probability but high magnitude harm with a high probability but low magnitude benefit? Article three of the universal declaration of humanrights that guarantees the right to life and article five that guarantees freedom from degrading or inhuman treatment are relevant here.

Selection of subjects

The principle of justice requires that research participants are selected fairly. Article two of the universal declaration deals with discrimination based on race, religion, nationality, social class etc. Based on this it can be argued that people have a right to participate in research. Furthermore, article 29 states that people have duties or obligations towards their communities.

Other recommendations

Always use the term 'participants' to describe those who participate in research, avoid using the term 'subjects'. 'Subjects' indicates unequal relationship, whereas participants indicate a relationship between equals. My response to people who say what is in a name is that the terms we use shape our attitudes and decision making. Though one of Shakespeare's plays has the line "A rose by any other name would smell as sweet" I would like to disagree. For example consider government spending on education and health, if you categorize this as spending on social overheads you would support moves to reduce these spending, but if this spending is categorized as investing in human capital you would support moves to increase these spending. We are more likely to protect the rights of participants in research than subjects of research.

Do not entrust the promotion of research ethics entirely in the hands of ERCs. The best way to promote research ethics is by empowering the participants.

When developing research proposals or even when reviewing proposals as a member of an ERC try to put you in the position of the research participants. I ask the simple question – "How would I react if I am invited to participate in this study?" or if I do not fit the eligibility criteria I ask the alternative question – "How would I feel if someone near or dear to me is invited to participate in this study?"

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References

De Silva, H. A., Pathmeswaran, A., Ranasinha, C. D., Jayamanne, S., Samarakoon, S. B., Hittharage, A., ... de Silva, H. J. (2011). Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Medicine, 8(5), e1000435. doi:10.1371/journal.pmed.1000435

Markel, H. (2004). "I swear by Apollo"--on taking the Hippocratic oath. The New England Journal of Medicine, 350(20), 2026–2029. doi:10.1056/NEJMp048092

Rothman, K. J. (1981). The rise and fall of epidemiology, 1950--2000 A.D. The New England Journal of Medicine, 304(10), 600–602. doi:10.1056/NEJM198103053041010

Samarawickrema, N., Pathmeswaran, A., Wickremasinghe, R., Peiris-John, R., Karunaratna, M., Buckley, N., ... de Silva, J. (2008). Fetal effects of environmental exposure of pregnant women to organophosphorus compounds in a rural farming community in Sri Lanka. Clinical Toxicology (Philadelphia, Pa.), 46(6), 489–95. doi:10.1080/15563650701837030

Shuster, E. (1997). Fifty Years Later: The Significance of the Nuremberg Code. New England Journal of Medicine, 337(20), 1436–1440. doi:10.1056/NEJM199711133372006

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). The Belmont Report: ethical principles and guidelines for the protection of

human subjects of research. U.S. Department of Health and Human Services.

UN. (1948). Universal Declaration of Human Rights.

Williams, J. R. (2008). The Declaration of Helsinki and public health. Bulletin of the World Health Organization, 86(8), 650–652. doi:10.2471/BLT.08.050955

World Medical Association. (2013). World Medical Association Declaration of Helsinki. JAMA, 310(20), 2191. doi:10.1001/jama.2013.281053