DRAFT Syllabus - "Research ethics"

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Content

Survey of ethical concerns in research involving human subjects including: historical perspectives on human subject research; ethical principles and guidelines for research and their comparison; frameworks for ethical review of research; ethical issues related to social and behavioral research, genetic research, and ethics of research in developing countries; and research ethics committee administration.

Objectives

1. to introduce students to the significance of human subject protection
2. to introduce students to ethical principles applied to research
3. to enable students to identify components of ethical review of research
4. to enable students to engage in current controversial ethical issues related to research
5. to enable students to engage in research ethics committee administration.

Duration ……

Detailed content

Week …….. *the significance of protection of human participants in research*

Research involving human subjects has become an important academic and commercial activity. The investment in basic science, clinical and public health research has yielded a great deal of progress in medical science and a steady decline in mortality and morbidity in recent decades. The more advance the medical technology have become, the more complicated the research methods have been. The public's perception of research is inevitably shaped by the way research is conducted. Recent events have brought about new concerns about research ethics every now and then. Society however entrusts investigators in scientific community with the privilege of using other humans to advance knowledge in science. Society, in return, expects that such generalizable knowledge will be for the common good and at the same time expects that such investigators will respect for the participants. The prospect of gaining such valuable scientific knowledge need not and should not be achieved at the expense of human rights or human dignity. A failure of human subject protection will definitely undermine the public trust and result in a slowness of medical progress. Although this is well aware by most investigators, for some, as history has shown, the quest for knowledge, the potential for personal fame and financial gain outweigh the respect for basic human rights.

Many historical events have accounted for research ethical concerns. From the time of Nuremberg trial of the Nazi leadership in 1945, a supplemental trial referred to as "The Nazi Doctors Trial" was held from Dec 1946 to August 1947. The judgment of the trial included a set of standards known as Nuremberg Code. The modern age of human subject protection is dated from such code. The standards have been accepted and expanded upon by the international research community. The statements in the code included issues for example:

informed consent of volunteers must be obtained; human experiments should be based upon prior animal experiment; the experiment should be justified by anticipated scientific results; only qualified scientists should conduct medical research; suffering and injury should be avoided; and there should be no expectation of death and disabling injury from the experiment. The Nuremberg code had been reconsidered and drafted by The World Medical Association (WMA) in 1953 and later known as the Declaration of Helsinki first issued in 1964. The Declaration defined rules for therapeutic and non-therapeutic research. The consent issue was repeatedly a requirement for non-therapeutic but not for the therapeutic research. It also allowed legal guardians to grant permission to enroll subjects. The declaration has been revised many times to keep it aligned with modern ethical issues and current research practices.

The legacy of Nuremberg trial has not stopped at the declaration of Helsinki. At the early 60s, Stanley Milgram, an American social psychologist, after studying the defense proposed at Nuremberg of "I was only following orders" became interested in "obedience to authority". He conducted a behavioral research recruiting adult volunteers for a study of "memory and learning". In experiment, the investigator instructed the subject to ask a third person a question and when the wrong answer was given, to administer punishment in the form of electric shocks in an increasing amount from 15 volts to 450 volts. Although, at some stage, the third person demanded the subject to stop and the subjects asked the investigator to stop, the investigator would insist the procedure should continue. At another point of experiment, the third person fell silent and non-responsive to questions and this was treated as wrong answer and punished. When the subject continued to seek permission from the investigator to stop, the subject was told that the experiment was important to complete for the advancement of science. Fully 60% of subjects were persuaded to administer shocks up to the highest level. The subjects were deceived about a number of things in this experiment. The third person was in fact a confederate of the investigator and only pretended to be hurt. No shock was really administered. The real aim of the experiment was to see how far the subject would go under the guise of complying with authority. The fact that some subjects experienced psychological stress and the deception involved posed important ethical concerns. First, not just physical harms but also psychological harms have to be considered. Second, informed consent has to be genuine. Finally, a position of authority over the potential subject leads to question whether consent is truly a voluntary decision especially in medical care setting, student-teacher, and employer-employee situations.

Another tragic historical event relating to human subject protection is the study of untreated syphilis in the Negro male, namely, the Tuskegee study. The study was started in 1932 by the U.S. Public Health Service which was later become CDC, and designed to investigate the effects of untreated disease. It evolved from genuine concern about minority health problem. At the time the only treatment available involved the use of heavy metal which was toxic to health. However, the subjects were not informed about the fact that the study would not benefit them directly. By 1951, penicillin was available as the treatment for syphilis but the subjects continued untreated because it was viewed as "never-again" scientific opportunity to study the natural history of syphilis. It was not until 1972 that the story was uncovered first by the press. The public trust towards scientific community was hugely damaged. The study was stopped in 1973 and the treatment was given as needed. As a result, in 1974, The National Research Act was developed and passed by the Congress. For protection of human subjects, the Act required informed consent and institutional review boards to review research and also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission later in 1979 published the "Belmont Report" which has become the cornerstone statement of ethical principles which most, if not all, research ethical guidelines have been based.

There have been many other tragedies and scandals directly or indirectly related to research involving human subjects. Among those, Willowbrook studies, The Jewish Chronic disease hospital study, and The study of skin treatment in prisoners had an impact on the issues of vulnerable subjects. Thalidomide tragedies in 60s posed an issue of the business practice of pharmaceutical company and quite recently in 1999 the gene transfer experiment which caused a death of young volunteer raised an issue of conflict of interest. The scandals have been spread to developing countries where external-sponsored researches mostly conducted such as Harvard Genetic study at Anhui province in China. This posed an issue of international concerns over inconsistent standard of research ethics concerns. With all those historical events, the research community as a whole suffers when a few investigators ignore basic principles of ethics. Compliance with human subject protection guidelines and regulations should be seen as the "right thing to do" rather than just the "requirement by the regulations". With this in mind, the right and welfare of human subjects can be protected and the public trust can be maintained.

Week …….. *ethical principles, regulations and guidelines*

A number of guidance has been developed since the declaration of Helsinki was first issued in 1964. Most of the existing guidance does not have the force of law. Many guidelines rather have persuasive force. Some have obligations imposed on signatory parties such as CIOMS. Others are at the level of law such as US FDA regulations or the protocol on biomedical research under the council of Europe's Convention on Human rights and Biomedicine. Generally, the codes consisting of rules are inadequate to cover complex situations. Those rules often come into conflict. They are frequently difficult to interpret or apply. Broader ethical principles on which specific rules are based will provide more flexible application in difficult situations. The most widely known ethical guidance related to research is *The Belmont Report.*

The Belmont report aims to provide analytical framework that will guide the resolution of ethical problems arising from research involving human subjects. The report consists of: a *distinction between research and clinical practice; three basic ethical principles and the application* of these principles. It is important to distinguish between research and practice of accepted therapy in order to know what activities should be reviewed by research ethics committee. The main aim of the practice is to enhance the well-being of an individual patient while that of the research is to develop generalizable knowledge. Research involves activities including the systematic collection or analysis of data with the intent to test a hypothesis, permit conclusion to be drawn, and thereby to develop or contribute to theories, principles, and statement of relationship; or revise or improve an existing theories, principles, or body of knowledge. If such knowledge involves application of drug, biologic, or medical devices, it can be called Clinical investigation or Clinical study/trial. Activities that designed with the intention of providing an immediate benefit to individual or their community should be considered as a practice. Those that have no direct or immediate benefit for the participants of their community, but that would be applicable elsewhere should be considered as a research. Program evaluation or quality improvement that the purposes are to assess the success of the established program or the results will be used to improve the program will not be a research by definition. However, when those is undertaken to test a new, modified, or previously untested intervention, service or program to determine whether it is effective and can be used elsewhere, they will be considered as a research by definition.

In research, investigators use those participating in research to produce knowledge that is of primary benefit of society. Thus, a potential conflict of interest always exists between

investigators' desire to pursue knowledge and their obligation to protect the rights and welfare of research participants. The line between practice and research if often blurred and both frequently occur simultaneously. The investigator's professional judgment is essential to maintain the integrity of the research process and to keep subjects informed of their role in the process and relationship with the investigator to prevent "therapeutic misconception".
Three basic principles of the Belmont Report are respect for persons, beneficence, and justice. The principle of *respect for persons* divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy-vulnerable populations. An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. Capability of self-determination depends on both the comprehension – understanding of given information, and voluntariness - free of coercion and undue influence. Vulnerable populations are individuals whose self-determination choices are, partly or fully, subject to coercion or undue influence. Vulnerability is closely related to autonomy. Because people are different in degree of understanding and also in extent to which they are influenced by others, their vulnerability is therefore not absolute. It implies a degree of limitation of capacity or voluntariness in relation to free decision making. In practice, vulnerability should be considered in lights of compromised ability to give informed consent, and of limited choice of alternatives outside the research settings. Vulnerability is sometimes considered in relation to decision made. Subjects' vulnerability should be an issue of concern whenever subjects seem to make high risk /low or no benefits decision. Their capacity to understand the information and their free self-determination choice should be questioned by board members in such case. However, the idea of considering vulnerability in relation to the decision made is still controversial and somehow difficult to put into practice. The application of the principle of respect for persons is a requirement of informed consent and protection of privacy and confidentiality.
Beneficence covers acts of kindness that express in actions of "do no harm" and "maximize possible benefits and minimize possible harms". The principle of beneficence involves Risk and Potential benefits. Risk is a probability and magnitude of possible harm or discomfort. Only risks that may result from the research will be applied in this guideline. Harms can be divided by type or by scale. Type of harms includes physical, psychological, legal, social, or economic. Harms can be at individual or at group level. Potential benefits can be to society, participants or to others. The benefit to society, that is to develop knowledge, is the primary goal of research. The benefits to participants may be directly from participation in certain type of research. For example: (1) receiving clinical significant information that could be used to influence the care provided; (2) receiving standard treatment as part of the research. They can be indirectly such as: experiencing increased social contact, sharing information with others, or gaining personal satisfaction from participating. Indirect benefits are not planned in research design and do not relate to the objectives of the study and they vary among research participants. Research can also benefit others such as institute, social groups, or communities. The application of the principle of beneficence is a requirement of scientific merit and assessment of risks and benefits.
The principle of *justice* requires fairness in distribution, that is, an equitable distribution of research burdens and benefits. It implies that the selection of subjects needs to be scrutinized in order to determine whether some class of subjects are selected simply because of their easy available or their compromised position. Justice demands also that research should not involve persons from group unlikely to benefit from the applications of the research.
Research should not use underprivileged persons to benefit the privileged. The principle of justice requires review of procedures for the selection of subjects and the outcomes of those procedures.

Although most guidelines share the principles they are based, many details differ. For example, the component of informed consent and the way consent is obtained are slightly different among guidelines such as Declaration of Helsinki, CIOMS, Committee on Bioethics of the Council of Europe, and also the US FDA. It is therefore worth comparing various issues regarding regulations adopted from different guidelines.

Week …… *components of ethical review of research*

There are at least three aspects of the ethical review of research, namely, review type, review process and content to be reviewed. *Review types* consist of: (1) Initial review which aims to assure the scientific validity and adequate provision for participants safety; (2) continuing review to assure ethic compliance by investigators and monitor the progress of the research including reports of number of subjects recruited, number of subjects still active, subject complaints, unanticipated problems, and adverse events; (3) review of serious and unexpected adverse events; and (4) review of proposed change of any part of the study. *Process of review* can be through the full board review or expedited review. Expedited review will be conducted by chair or experienced board member whom appointed by chair of the research ethics committee. Protocols that can be reviewed through expedited process are those which the research activities that present no more than minimal risk; If identification of the subjects or their responses place them at risk, the reasonable and appropriate protection must be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal; minor changes in previous approved research which no additional risks involved; recruitment materials which the standard requirements of informed consent have been applied. *Content to be reviewed* consists of: (1) *scientific value and validity* which include statements addressing magnitude of the problem, impact of expected results on health or welfare of target population, rational of the study, design able to provide desired answers, feasible and scientifically reasonable methods, samples that represent target population, appropriate statistics analytic plan, adequate monitoring plan; (2) *ethical review* which include procedures ensure that risks are minimized, risks are reasonable in relation to benefits and knowledge gain, additional safeguard is put in place for the vulnerable, inform consent is sought, inform consent is properly documented, privacy and confidentiality are protected, data safety and monitoring are planned, equitable selection of subjects is guaranteed, and local community concerns are considered; (3) *qualification of investigator* together with an adequate and appropriate time, staff, and facility to carry out the proposed research, also an acceptable and manageable conflict of interest; (4) *informed consent* which covers elements such as statement that the study involves research, explanation the purpose, expected duration of subjects' participation, description of procedures, description of any reasonable foreseeable risks or discomforts, description of any anticipated benefits, statement about the extent of confidentiality, statement that the participation is voluntary, refusal will be respect, discontinuation is possible at anytime without any adversary, explanation of the contact person to answer questions, agreement by subject's signature and person who obtains the consent, additional elements can include alternative procedures, cost, compensation, significant new findings, number of subjects, randomization and placebo assignment, legally authorized representative's consent, subject's assent, etc…as approppiate; and (5) *recruitment materials* which general standard of informed consent applies.

Week …….. *controversial issues related to ethics in research*

Many ethical issues related to research are still controversial. Among those, review of social and behavioral research, research involving genetic material, and ethics of research in developing countries are currently challenging.

Social and behavioral research (SBR) focuses not specifically on biomedical, but rather on the areas of attitudes, beliefs, and behavior. SBR applies data collection methods such as questionnaires, interviews, focus groups, direct observation, and non-invasive physical measurements. Although most SBR poses little potential for physical discomfort or harm, SBR usually carries the possibility of stress, emotional/psychological effects, loss of confidentiality, and other risks. In addition to direct emotional harm, risks from research can include impingement of rights, privacy, and autonomy. Data collection via the Internet (either e-mail or Web) cannot be considered confidential, even with a "secure" server. Transmission and storage technologies are not reliably secure, and messages might not be anonymous even when they appear to be. Prospective subjects need to be informed of the risk associated with research conducted over the Internet. Compared to biomedical research, the potential risks and distress are much less obvious and harder to predict. As a consequence, it is often difficult to devise strategies that adequately protect participants. Further, the resulting harms (for example, emotional distress from being asked about childhood abuse) might be more difficult to correct. Reporting of adverse events or reactions is as important in SBR as in any other type of research.

Sometimes people provide data about the subjects of a study (e.g., teachers filling out surveys about their students, health care providers answering questions about their patients). Suppliers of research information are considered as subjects, even though they are not themselves the focus of the research, and should be treated as such. The opposite situation occurs when the main subject provides information about other people (such as friends or family members), for inclusion in the research data. All people about whom research information is gathered are considered to be research subjects. The REC should consider whether to require informed consent from these "secondary subjects."

Genetics research raises ethical issues that differ in many ways from those that arise in other kinds of human subjects research. For a number of reasons, including increased risk of bias, discrimination and stigma, genetic privacy and confidentiality are sometimes thought to be more important than privacy and confidentiality in other kinds of research. Genetic formation is for these reasons sometimes likened to information about sexually transmitted diseases or mental health problems. Investigators preparing to conduct genetic analyses must tell potential subjects which entities and persons will have access to the data. This might include investigators at other institutions, corporate sponsors, a government, employers, insurance companies, etc. If information obtained during research will be placed in a patient's medical record, this too must be disclosed. Subjects must also be told of the risks of an employer or insurer having access to an individual's genetic information. Unlike most other kinds of health data, genetic information applies to or is about more than one person. Analyze genomes and you will learn something about a person's parents, siblings, children, and perhaps others. This means that individuals can lose privacy and/or confidentiality even if they are not the source of the specimen or information being studied.

Research on stored biological samples allows investigators to conduct studies long after the subject has moved on. It is helpful to think of research on stored samples as two kinds: Retrospective, in which investigators use blood, tissue, etc. from pre-existing collections, and Prospective, in which investigators collect samples to create new banks. If the research is retrospective and adequate steps to prevent identification of the samples' sources are taken,

then genetic research can often proceed without requiring that individual subjects provide valid consent. The benefits of such research can be quite valuable and may outweigh the violation of the principle of obtaining informed consent from all the sources of stored biological samples. It is however possible to inform prospective sources/subjects that their tissue will be banked for future, unspecified research, but this is increasingly difficult. Will the samples be used for research in cancer genetics or behavioral genetics? Will results be correlated by race or ethnicity? Will the results be used to develop proprietary products? These are all questions that subjects increasingly want answered before they consent to participate in research. The secondary use of tissues is emerging as one of the greatest challenges of genetic research. Researchers need to consider how much information is adequate at the outset to permit subsequent analysis to be conducted without additional consent.

Research conducted in developing countries often is externally sponsored research. This poses many concerns such as difference in standard of care, research that is irrelevant to health problems in host countries, and cultural differences in consent process. Standard of care refers to treatment provided to participants in research. The level of care provided to control group in clinical trials is the subject of controversy. Should it be the best available treatment anywhere in the world or the treatment based on an alternative standard currently available in host countries? Setting priorities for health-related research is another concerns. It is important in developing countries because national resources are limited. Many developing countries do not have capacity to set their own priorities for research. Many external sponsors also fail to take diseases that are a national priority into account. Therefore, the populations in which the research is carried out do not stand to benefit. Regarding consent issue, many participants in developing countries believe the research may be the only means of receiving health care or other benefits. When medical care is combined with research, there must be a rigorous process for obtaining consent and participants must be made aware of the exact purpose of research. Moreover, certain standard procedures for consent in developed countries may be inappropriate in some developing countries, due to the differences in social and cultural environments.

Week …….. *research ethics committee administration*

Basic protections for human subjects are research ethics committee (REC) responsible for review of research; investigator responsible for obtaining informed consent of subjects; and institute responsible for support of human subject protection program and compliance with applied regulations. However, there are many challenges that face the current oversight system. For example: (1) lack of adequate resources both financial and human; (2) lack of clear and consistent regulations; (3) enforcement weakness-no clear line of authority, limited repertoire of sanction to match the range of possible violations; (4) overemphasis on procedural requirements rather than ethical principles (so investigators and REC exercise in avoiding sanction and liability rather than pursuing appropriate ethical standard-moral excellence); (5) regulations not adequately addressing all types of research such as social science research; (6) REC burden of excessive work but lack of basic resources such as staff, space, and technology and also financial and academic support for REC members; (7) multi-site research and lack of consistency among local RECs; (8) education needs for REC members and investigators. All above mentioned lead investigators to view the oversight system as irritating obstacles to doing valuable work. REC who implement the regulations become frustrated with investigators resistance. Investigators might avoid submitting research

protocols or fail to disclose certain aspects of the protocol. This could place participants at risk and compromise public trust in the oversight system. The system should ensure the protection of participants in a manner that encourages and facilitates research that is consistent with accepted ethical principles. To help investigator and REC to fulfill their responsibilities, the institute and the higher governmental bodies should promote the development of education, certification, and accreditation systems that apply to all investigators, REC members, and institutes.

For REC, there should be **written procedures** which state clearly about: *(1) authority of the board given by the institute* to review and approve the research protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documentation informed consent of the research subjects, require modifications in (to secure approval) or disapprove all research activities involving human subjects, and the authority to review progress of studies at intervals appropriate to the degree of risk to human subjects, to suspend or terminate approval of any study that has an unanticipated problem involving risks to human subjects, serious or continuing noncompliance with any applicable regulatory requirements or the requirements or determinations of the Board*; (2) organization and membership of the boards* that guarantee qualification of members and membership diversity; *(3) management of the boards* which includes selection and appointment, terms and service, and duties of both chair of the committee and also the committee members; *(4) functions of the boards* with regard to research review procedure and how the committee exert her authority *(5) operations of the boards* concerning meeting scheduling, voting requirement, and communication of the committee; and finally *(6) board record requirements* dealing with minutes and record keeping. The written procedures are necessary for quality assurance and improvement. Apart from that, pre and post meeting operation should be effectively planned and executed. Submission forms and process should be made practical to investigators. Letter of approval and other correspondences should be provided to investigators in timely fashion.