Ethical Challenges of Research

1. Learning Objectives

After reviewing this chapter readers should be able to:

- Understand why ethics is important to research;
- Identify codes of ethics that address research;
- Describe the Belmont Principles;
- Identify some issues surrounding the Belmont Principles today;
- Understand the roles of research ethics committees;
- Identify some issues surrounding research ethics committees; and
- Identify other elements critical to responsible conduct of research.

2. Introduction

What does ethics have to do with research?

Ethical codes or principles are an expression of how we should behave as individuals and as a society. They are moral judgments that can be applied to particular situations to help us make decisions and guide our behavior. Inevitably, they are linked to cultural values at a particular time in our history and are subject to change as attitudes and values evolve. What was normative just a half century ago, may be considered insensitive today.

In research there may be a conflict between the expeditious conduct of a study and the burdens of doing what is respectful to animals or humans. On the one hand, researchers are focused on expanding knowledge and on the methodology of their projects such as subject selection, sample size, research protocols, statistical analysis, equipment, and personnel. At the same time, as inherently responsible persons, they try to respect the research environment, which requires attention to the appropriate use not only of physical resources including funds, but also to human and animal subjects.

Aside from direct treatment of human and non-human subjects, how research is conducted is an important aspect of whether or not it is ethical. For example, strict adherence to the research design, protocol and analytic plan is critical to data integrity. Avoidance or disclosure of financial and/or personal conflicts of interest may affect subject recruitment as well real or perceived objectivity or bias in recruitment and in analysis and reporting results. These aspects of research behavior, along with adherence to accepted scientific practice, such as honesty in authorship, data collection, analyses and reporting, avoiding conflicts of interest of reviewers, avoiding misconduct and misbehavior and reporting it if present, all contribute to whether research is ethical.

Only when the research is of sufficient quality to potentially contribute to knowledge can we justify involving humans or animals and utilizing other resources. Ethical considerations may help us decide whether the research should even be done, and if so, how it should be pursued.

How we conduct our scientific endeavors not only affects those directly involved, but also the public's perception of science and scientists. Results from research provide a basis for further studies, and in addition may influence public policy and legislation. Challenges to scientific integrity can erode public confidence and belief in findings. Therefore, it is important to be transparent, competent, honest, and follow ethical guidelines in regard to research subjects.

2. Introduction

Welfare of Human Subjects

The first modern code governing ethics of research was developed during the Nuremburg trials of Nazi war crimes in response to abuses during medical experimentation on humans. Subsequently, there was concern with protection of human subjects of research in the US in the 1950s and 1960s. Media reports about abuses during research stimulated legislation that led to the development of ethical principles and regulations.

Standards for use of animals in research have also been developed.

Environmental Safety and Protection

Environmental exposure that imposed risk of harm stimulated workplace welfare provisions in such areas as radiation safety, chemicals, biologic pathogens, ergonomics. OSHA Hazard Communication Standard (29 CFR 1910.1200) and Occupational Exposure to Hazardous Chemicals in Laboratories (29 CFR 1910.1450). OSHA Bloodborne Pathogen standard (29 CFR 1910.1030). Many institutions provide on-line training in laboratory and workplace safety.

Ethical principles, codes of ethics and oversight of research provide guidance. However, continuing attention to research conduct is needed in view of the fact that a meta-analysis of survey studies found that 30-74% of respondents report that they have been involved in or observed inappropriate behavior in the conduct of research (Fanelli, 2009).

3. Principles, Codes, and Standards Today

The Nuremburg Code

The Nuremburg Code, developed as a result of Nazi war crimes, was the first modern publication of ethical guidelines for experimentation with humans. It states an explicit requirement for voluntary consent of research subjects and spells out the elements of that consent. The code stipulates that the use of human participants is permissible (justified) so long as:

- human subjects are necessary
- the results hold promise of benefit to society
- scientific basis and design are sound
- harms to humans are minimized or avoided
- risks are minimized, experimenters are qualified
- voluntary withdrawal of subjects is allowed and that the research will be terminated if research subjects are likely to be injured or harmed.

- **The Nuremburg Code**
- **The Declaration of Helsinki**
- **The Belmont Report and The US Code of Federal Regulations: The Common Rule**
- **The Council of International Organizations of Medical Science (CIOMS)**
- **International Conference for Harmonization Guidelines for Good Clinical Practice (GCP)**
- **Standards and Operational Guidance for Health Related Research**

3. Principles, Codes, and Standards Today

The Declaration of Helsinki

The Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, was developed by the World Medical Association in 1964 and has been revised repeatedly, most recently in 2008. It declares the necessity of research with humans, physicians' duty to safeguard health and privacy, puts human well-being before scientific advances, and requires consent free of coercion.

It includes principles for research including:

- sound science
- protection of human dignity
- ethics committee review and oversight
- risk benefit assessment and potential benefits outweigh risks of harm and risk can be managed
- the research is important and likely to benefit the subject population
- participation is voluntary and subjects are fully informed

The Declaration of Helsinki addresses situations in which consent is not possible, the need to share research outcomes by publishing them, and the handling of situations in which research is combined with medical care.

The Belmont Report and The US Code of Federal Regulations: The Common Rule

The Belmont Report, published in 1974, is a statement of ethical principles governing research with humans developed by the US Congressionally appointed Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It identifies three ethical principles: respect for persons, beneficence, and distributive justice. The Belmont principles have been codified into Regulations and the Common Rule and have been adopted in whole or part by nineteen US federal agencies to regulate research with humans conducted or supported by the US government. Revisions to the Common Rule were proposed in July 2011. The proposed changes, responses to public comments, and the final revision will be available on the website of the Office Human Research Protections.

3. Principles, Codes, and Standards Today

The Council for International Organization of Medical Sciences

The Council for International Organizations of Medical Sciences (CIOMS) was founded by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. In the 1970s CIOMS and WHO worked on guidelines to indicate how the ethical principles articulated in the Declaration of Helsinki could be applied to research with humans, especially in developing countries. As new research methods and practices emerged, particularly the expansion of clinical trials in developing countries, conferences were held to address issues that were not covered in the original guidelines. In 2002, CIOMS published ethical principles (they adopted the principles in The Belmont Report) and 21 guidelines that are broadly applicable, including in low resource countries. They cover

- ethical justification of the research,
- scientific validity,
- ethics committee review,
- informed consent and situations when consent is not attainable,
- inducements to participate in research,
- risks and benefits,
- research with low resource populations,
- choice of control groups in clinical trials,
- research with vulnerable groups,
- confidentiality,
- compensation for injury in research,
- strengthening infrastructure in developing countries, and
- ethical obligation to provide health services.

Each Guideline is accompanied by commentary. In 2009, an update issued Guidelines for epidemiological research was published. For updates see http://www.cioms.ch.

3. The Conceptual Phase

International Conference for Harmonization Guidelines for Good Clinical Practice (GCP)

Good Clinical Practice Guidelines were developed by the International Conference on Harmonization (ICH). Governments can use them to develop regulations governing clinical trials with humans. They include protection of human rights, standards for conduct of trials, and responsibilities and roles of sponsors, investigators, monitors and clinical research associates. When adhered to, the results of trials conducted multi-nationally should be acceptable for safety and efficacy decisions by all participating governments. In 2005, a Handbook for Good Clinical Practice was published and in 2009 an on-line course became available.

Standards and Operational Guidance for Health Related Research

The “Standards and Operational Guidance for Health Related Research” is a draft document released for comment in 2011 by the WHO. This document is more specific than general ethical guidelines and is intended to govern the establishment and operation of research ethics committees that review research with human subjects.

Exercise 1

Match each of the important events in the box on the right with the correct description along the timeline.

TIMELINE:

1949 – The first widely adopted published ethical guidelines for research with humans, developed as a result of Nazi war crimes.

1964 – Developed by the World Medical Association; addresses physicians' duty to safeguard human subjects above scientific advances, and principles for weighing risk and harm.

1974 – Statement of principles for human subject research, since codified into Regulations and Common Law; principles include: Respect for Persons, Beneficence, and Justice.

1970s – Developed with the World Health Organization; a set of guidelines for applying ethical principles to research with human subjects in developing countries.

2005 – Published to develop regulations governing clinical trials with humans.

IMPORTANT EVENTS:

- The Declaration of Helsinki
- The Council for International Organization of Medical Sciences (CIOMS)
- Good Clinical Practice Guidelines
- The Nuremburg Code
- The Belmont Report

4. The Belmont Principles

In the U.S. the ethical principles of The Belmont Report are the ones described in the Federal Regulations and most widely adopted as ethical guidelines.

The Belmont Report includes three ethical principles:

THE BELMONT REPORT
Respect for Persons
Does the planned research respect the autonomy of human participants? Respect for persons assumes that people are able to make informed decisions about whether or not to participate in research. Researchers are to provide enough information so that an informed, voluntary decision can be made. Whatever the decision of the potential research participant, that choice should be respected. Moreover, if a person decides to withdraw from research participation, that decision is to be respected. The principle, respect for persons, is implemented as voluntary informed consent to participate in research. If people with diminished or limited autonomy, such as children, some cognitively impaired people, those in a coercive environment, those with compromised consciousness or other vulnerabilities are to be involved in research, additional protections are required. How much protection is needed is a function of the risk of harm and the likelihood of benefit.
Beneficence
Beneficence, in the context of research with humans, means to do no harm, minimize risk of harm and maximize the benefits of research to protect human welfare. Investigators have the responsibility of analyzing the risks and benefits. If the probability and/or magnitude of harm is not outweighed the benefits, the risks must be justified in terms of the importance of the research for the participants and/or society. Assessment of risks and benefits often is difficult. Both occur along a spectrum. They may be direct or indirect, immediate or for future persons in similar circumstances. They may be physical, psychological, social or economic and may be perceived differently by persons with differing interests. An assessment of risks and benefits is also done by the ethics review committee

members who consider scientific merit and importance, competency and experience of the research team, and appropriateness of the subject population for risks (including threats to privacy and confidentiality) and benefits.
Justice
Justice relates to fair and equitable distribution of benefits and burdens of research. Practically, it means that research participants are selected fairly, with all segments of the population having an opportunity to be included in a study, provided that inclusion is scientifically and ethically justifiable.

4. The Belmont Principles

Informed Consent

The principle of Respect for Persons states that researchers are to provide enough information so that an informed, voluntary decision can be made. This is known as Informed Consent.
Elements of Informed Consent from The Belmont Report are:

- Information
- Comprehension
- Voluntariness

Additional elements of informed consent.

When appropriate, one or more of the following elements of information shall also be provided to each subject:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
- The approximate number of subjects involved in the study.

The Code of Federal Regulations spells out the elements of informed consent more fully.

5. Current and Unresolved Issues

The Belmont Principles were intended as ethical guidelines. Application of each principle by the research investigators and by the ethics review committee requires judgment, interpretation and ethical analysis in the context of a given situation, e.g. a specific research proposal and cultural context. Ethical dilemmas arise in situations in which ethical principles conflict. Both science and social attitudes have changed in the 40 years since the Belmont Report was published. Interpretation of the principles and accepted opinion about what constitutes ethical behavior has evolved. Research is conducted on a global scale, and has become increasingly complex and integrative. There is now greater diversity within research environments, and more attention to community engagement and the potential value of the research to the community.

These issues have stimulated debate about whether the Belmont Principles are sufficient and appropriate guidelines to protect human subjects and about whether ethics review committees —the main system for approval and oversight of human welfare in research — have become too burdensome. The proposed changes to the Common Rule are designed to address these concerns and changes in the scientific landscape. As society and research practices change, ethical issues persist. Some of the major current issues will follow.

5. Current and Unresolved Issues

Consent

What constitutes valid informed consent?

The principle, respect for persons, is implemented through voluntary informed consent. The elements of informed consent are stated in the Code of Federal Regulations.

The Code of Federal Regulations states that Informed Consent should include:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others, which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Consent requires that adequate information is given to allow research participants to make an informed decision. Most agree this requires a determination that the potential subject has the capacity to consent, along with disclosure of the research purposes and procedures, risks and

benefits and alternative procedures available. Participants must be informed that they can withdraw from the research without penalty, and that confidentiality will be maintained. But, how much information should be disclosed? How should it be communicated? How does one assure comprehension? How much does a reasonable person want to know? Investigators are faced with the ethical dilemma of providing enough information to allow a potential research participant to make an informed choice but not providing so much information that the potential subject is overwhelmed or scared away, or that the results are compromised.

Example 1

To develop a curriculum module to educate teens about consequences of substance use and abuse, research staff recruit teens and parents to participate in focus groups. The focus groups are tasked with identifying knowledge content (i.e. what teens need to know). Each study participant is to be paid $20 at the end of each session. After lively discussion at the first focus group sessions, the researchers are surprised that only 20% of parents and 10% of teens return for the second session. When they phone the no-shows, the researchers learn that several participants are concerned that sharing their knowledge about the local drug scene and drug use may suggest that they are too involved for comfort and may get into trouble with authorities. The researchers promise confidentiality, urge continuation in the study and double the incentive to $40. A day prior to the third scheduled focus group meeting, the investigators phone the no-shows again. They make it clear that they have the option of dropping out but repeat that discussions are confidential and that they consider input from people who know the teens drug use and the local community important to the development of a valid educational program on drug use and abuse. How many times should investigators ask subjects to continue in a study? Are the researchers improperly coercing the participants? In this example, can confidentiality be assured?

5. Current and Unresolved Issues

Consent

Example 2

A group of academic institutions are collaborating on a survey study of alcohol consumption by students. They develop a common protocol. During the consent process, participants are informed of the purpose of the study and the methods. They are asked to voluntarily respond to a questionnaire about social activities and drinking behavior. Because some of the students are below legal drinking age and because some of the institutions prohibit alcohol on campus, the investigators plan to obtain a certificate of confidentiality prior to starting data collection. The purpose of the certificate is explained during the consent process along with its limitations. Each institution's IRB is to review the study and each institution is to apply for a Certificate of Confidentiality. The study begins. Of the participating institutions, one fails to apply for and obtain the Certificate of Confidentiality. What is the issue? Is the consent valid?

Empirical research on the consent process indicates that research participants often may not understand enough about research to make a fully informed decision. Concepts such as randomization, controls and double blinding are particularly difficult. Many subjects believe that there will be therapeutic benefit from participating in research (Applebaum, Roth, & Lidz, 1982; Applebaum, Lidz, & Grisso, 2004; Pace et al., 2005).

More information than can be retained often is included in consent forms. Research also shows that subjects prefer short consent forms to very detailed ones, though there is some indication that both satisfaction and comprehension are similar (Stunkel et al., 2010).

Is Consent Informed?

- In a clinical trial of a drug for cancer, 30% of participants reported that they were receiving an unproven drug. 70% believed that the drug was the best therapy for their cancer (Joffe et al., 2001).
- In a questionnaire study, caretakers/parents who brought a child to an emergency room for treatment were queried about their willingness to enroll a child in research. More were willing to have their child participate in a research study than in a research project,

research experiment, medical experiment or medical study. Only 18% responded that the choices were equivalent. A research study or project was perceived as safer while the words medical and experiment were associated with higher risk and unproven treatment (Cico, Vogeley, & Doyle, 2011).

- When comparing a video presentation with a written explanation, more people who saw the video correctly reported the purpose of Phase I. trials. In both groups, a majority thought that Phase I. related to efficacy rather than safety and that their doctor thought they might benefit from the drug (Kass et al., 2009).
- A study of Phase I drug testing consent forms reported that virtually all stated clearly that the study was research, that its goal was to test the drug for safety, and addressed benefits and risks. However, 96% of the forms also referred to the drug as treatment or therapy without reference to research or the agent's experimental nature. (Horng et al., 2002).
- Readability of consent forms analyzed with the Flesch-Kincaid Scale was 10.6, 2.8 grade levels above the recommended reading level (Paasche-Orlow, Taylor, & Brancati, 2003). A recent study of consent forms for HIV trials reported median readability was 9.2 – 12.2 grade level, depending on section. Median length of all forms was 22.4 pages. This clearly is more information than most people can process and remember (Kass et al., 2011).

Exercise 2

For each example below, decide which of the three principles from the Belmont Report is most relevant.

	Respect for Persons	Beneficence	Justice
For a condition that affects population subgroups differentially, an investigator strategizes to include neighborhoods with large minority populations in order to recruit a diverse sample into her study. She meets with neighborhood residents to explain the study and to encourage broad participation.	☐	☐	☐

	Respect for Persons	Beneficence	Justice
A research subject consents to research but halfway through the research says he has to leave and does not wish to continue.	☐	☐	☐

	Respect for Persons	Beneficence	Justice
In research on cardiac function and aging, participants between the ages of 70-80 are recruited. The investigator meets with each participant for 5-10 minutes, and describes the research. The researcher gives the potential participant a consent form to read and sign, and while leaving the room says that he will be back to pick up the form and begin the research in 10 minutes. The consent form is 8 point type and 9 pages long.	☐	☐	☐

	Respect for Persons	Beneficence	Justice
A study to investigate the effects of prolonged hypothermia recruits normal volunteers and excludes potential participants with a history of heatstroke, seizures, heart disease, or stroke.	☐	☐	☐

	Respect for Persons	Beneficence	Justice
A research procedure to halt bleeding in the brain following head trauma has been found in animal trials to be more effective than currently used interventions. An IRB is reviewing a proposal to use the experimental procedure in humans during emergency transport, to monitor the research subjects closely and to follow with accepted treatment as indicated. The study will use a randomized design. It is anticipated that the subjects will be unconscious and unable to consent.	☐	☐	☐

	Respect for Persons	Beneficence	Justice
A cognitively impaired person has consented to longitudinal research on cognitive impairment. During the third follow-up, the participant turns away, paces in the room, and appears anxious and agitated. The investigator asks for assent and the subject appears to nod 'No'.	☐	☐	☐

5. Current and Unresolved Issues

Consent

Individual and/or Community Consent

Today, research is seen as a collaborative partnership between investigators, participants and their institutions. Implementation of the principle of respect for persons has come to include engaging communities in research and negotiating community consent. In today's environment, it is considered good practice to have community involvement during every phase of research from planning to reporting. However, who is the community? Communities differ in their organization and cultural traditions. When an investigator is studying a community or group rather than the individual, who shall consent for the group? Is group and individual consent appropriate? Is it more effective to discuss research and answer questions in an individual or group setting?

Example 3

Research with Native Americans may require tribal as well as individual consent. Researchers had discussed a potential research project on diet, exercise and aging with tribal leaders. The tribal council suggested a listening circle to discuss the research with tribal elders. Tribal elders asked how the research would benefit their tribe and made it clear that benefit was a condition of their participation. Discussion focused on obesity-related diseases that are common among tribal members. The researchers indicated that they could not promise benefit and if there were some benefit resulting from the research, it would likely be in the future and not accrue to research participants. The tribal elders explained that their perception of benefit means it should be within seven generations. They recommended that the research proceed.

5. Current and Unresolved Issues

Consent

Consent for future research

Other issues involve consent for research that will extend over a period of time. In doing research on degenerative diseases, e.g. Alzheimer's disease, we do not know that a person who consented when competent is willing to continue participation in research after s/he has experienced cognitive and emotional changes and whose cognitive capacity is questionable. In such situations a research advance directive may be helpful. A research partner or other person may be able to give substitute or surrogate consent and/or, as an advocate who knows the person well, judge whether the advance directive should be followed. In such situations, the consent process should include information on whether the data can be used if the participant withdraws from the research, and whether follow-up information can be sought.

Example 4

A person with mild cognitive impairment and a family history of Alzheimer's Disease is a research participant who has consented to longitudinal cognitive testing. Years later the disease has progressed. During the testing session, the participant is agitated and objects to the research. Should the cognitive testing continue?

Specimens collected at one point in time may be used later for purposes not known at the time of consent. Is this ethical? Can a research participant give consent for future use of specimens or data when the purpose of the future research is not known?

5. Current and Unresolved Issues

Consent

Research is a process during which participants may have questions, change their minds or reconsider their participation. Disease processes may change the situation or cognitive capacity of the participant. Respect for persons requires that investigators engage in ongoing discussion about the research, respond to questions honestly and to the fullest extent possible, and respect participants who decide to withdraw from research or to change the terms of their participation.

Conflicts among ethical principles may arise. For example, ethical conduct of research requires that the investigators adhere to their research plan and to their recruitment plan for selection and retention of subjects so that valid analyses can be done. Investigators have an interest in completing the research as planned, yet this may not be possible if identifiable subsets of subjects do not consent or withdraw from the research prior to its completion. The investigators are confronted with the ethical dilemma of altering the recruitment plan which may introduce bias or a systematic effect, changing recruitment incentives, or compromising the consent process by withholding information that makes recruitment or retention more difficult. They may modify their research aims and work with a more limited sample. Alternatively, they may recruit more subjects to achieve their research aims. Such changes might mean a longer time to complete the research and/or difficulty achieving the sample at the projected budget.

5. Current and Unresolved Issues

Beneficence

Risk/benefit assessment:

An assessment of risk/benefit is done by the investigator and by the ethics review committee. That assessment most often is a judgment. Although it may be informed by expert opinion, the literature and current best practices, there is rarely an objective metric to make the assessment. Different investigators, community groups and/or ethics committees may come up with different assessments. This can present problems and cause delays, particularly for multi-site research.

Rid and Wendler's Guidance for Risk/Benefit Assessment

- The research is scientifically sound so that valuable knowledge may result
- The proposed intervention(s) are necessary to achieving the research goals.
- Evaluate the risk of harm to subjects on the basis of existing data and subject characteristics.
- Evaluate the probability and magnitude of possible benefits to subjects on the basis of existing data and subject characteristics.
- Evaluate whether research benefits outweigh risks or vice versa on the basis of data and best judgment.
- Assess whether risks are justified by potential benefits using available data and expert experience.
- Evaluate whether risks are justified by the potential value of the research (Rid & Wendler, 2011).

Balancing risk of harm against potential direct or future benefit

There may be risk of harm to find out whether the research has potential for benefit. Despite efforts made to design research to minimize risk of harm and maximize benefit, if any, there may be known or unanticipated harms. There also are differences among subjects in perception of risk and benefit and in actual risk and benefit as a function of the subject's condition or situation.

Example 5

A. Military action is occurring in hot climates. It is important to military leadership to study the impact of temperature on performance. Healthy volunteer college students are recruited to exercise on a treadmill wearing a 50 pound backpack at an ambient temperature of 110 degrees. They are to walk at 4.5 miles/hr for one hour or until they reach a pre-determined maximum heart rate. How would you assess the risk/benefit? Are there special precautions that you would take?

B. A terminally ill person consents to undergo a risky experimental therapy that has potential benefit to others in the future. How does one assess the risk/benefit ratio? It may be very different for the individual and for society. If the therapy is effective and the subject is still alive, do the researchers have an obligation to offer it to the subject when the research is completed?

5. Current and Unresolved Issues

Beneficence

Special protections for vulnerable people:

When research is considered to be important and sound but to have more than minimal risk, an ethics review committee may recommend special protections. For example, based on the level and probability of risk, the ethics committee may monitor the research procedures, monitor the consent process, appoint a research partner/advocate, approve the research to be done with a few subjects and then reassess the situation, re-review the research more often than annually, and/or ask the investigator to report back to the ethics committee on research progress and problems. Sometimes, because of risk of harm, a subject population is judged to be inappropriate for inclusion and a different population must be found. Special protections and selection of subjects reflects the application of respect for persons, beneficence and justice.

Example 6

The National Children's Study recruits pregnant women and follows them and their offspring through childhood and adolescence and beyond. Pregnant women and children are considered vulnerable subjects that require special protections. Pregnant women and their children are subject to physical, psychosocial, environmental and educational observations according to protocol. During the study, some subjects are observed to be in a dangerous home situation, e.g. exposed to violence and abuse. For other participants, environmental hazards are identified in laboratory analyses, e.g. dangerous lead levels. This is an observational study, not an intervention study. Do the researchers have an ethical responsibility to intervene if an environmental hazard is identified? What protections might you provide? What are the ethical responsibilities of the researchers in this situation?

This study is referred to a specially convened national committee for ethics review and approval. The committee can serve as a resource as well as a central IRB. Each research site, if a harmful situation is identified, e.g. elevated lead level, can make a referral so that an appropriate intervention is implemented. The study planning and oversight groups work to anticipate ethical and other issues and to address those issues. For example, when the children in the study reach majority age, their consent to continue in the study will need to be obtained.

Research in developing countries.

Since publication of the Belmont Report, research conducted on a global scale has increased. Concern that research participants in resource poor countries not be exploited has resulted in attention to benefits such as infrastructure support, education and training, and health care in health-related research. Also, it has stimulated research on incentives that are not coercive and on how best to obtain informed consent from groups that may be unaccustomed to being asked for or are unfamiliar with the concept of consent. Such efforts to provide benefit for research subjects are guided by concerns about exploitation and other ethical considerations, specifically providing benefits.

5. Current and Unresolved Issues

Justice:

Inclusion of vulnerable subjects:

The Belmont Report and the other reports of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (NCPHSBBR) were published shortly after revelations about abuses in the government sponsored Tuskegee study of syphilis. In response, the public attitude, reflected in hearings and the press, favored exclusion, extra protections and/or strict conditions under which vulnerable individuals or groups could participate in research. In recent years there have been more revelations about abuses of human research participants that occurred prior to publication of The Belmont Report, enactment of the regulations and wide-spread use of research ethics committees.

Those who participate in research bear the burdens and should reap the benefits, if any. This principle has been interpreted to mean that research should relate to the problems experienced by the subject population. During the last quarter of the 20th century, advocacy movements gained strength. The Breast Cancer Coalition and Act Up, an AIDS advocacy group, argued in favor of participation in research of people who might gain direct benefit from that research. At the same time it was proposed that vulnerable groups be included in research, it was posited that they and those who represent and/or understand them, whenever possible, should be included as reviewers of the research and should have a voice in deciding which research is to be done, especially if the research is publically funded.

Social attitudes moved from exclusion of vulnerable subject groups to inclusion, based on the principle of justice, i.e. just distribution of benefits and burdens. The Belmont Report and the regulations that followed leave it to the IRB to define just distribution of benefits and burdens and to find the balance between inclusion of subjects from all relevant groups and appropriate protections. The federal policy that mandates inclusion of women and minorities in all NIH-supported and conducted clinical research reflects evolution of the principle of justice toward inclusion.

5. Current and Unresolved Issues

Justice:

Delivery of care / Standard of care:

In research that involves delivery of health care, the benefits often involve providing care during and after the research. Defining a fair standard of care may be problematic. Does care need to be equivalent to the best standard of care anywhere or reflect the local standard of care? How does one assure voluntary participation when research-related care may be the only care available?

Example 6

Randomized clinical trials with antiretroviral drugs are conducted in African countries that have a high rate of HIV/AIDS. The drugs promise to be effective. When the research is completed, are the researchers and/or drug companies ethically obligated to continue treatment for experimental subjects and to provide treatment for control subjects? Who should pay for the drug, manage its distribution and supervise its administration?

Compensation:

Participants in research generally are reimbursed for expenses related to their participation, e.g. travel, meals and child or elder care. They also may be compensated for time, inconvenience and for risks they accept as part of the research. Determining a just level of compensation, and particularly one that is not an undue inducement or coercive for poor and/or disadvantaged research subjects, is another issue. When conducting research with children, with decisionally impaired adults, or with a community, who should be compensated?

5. Current and Unresolved Issues

Privacy and Confidentiality:

Protection of human welfare may involve an assurance that identifiable information about participation in research will be protected along with identifiable research data. Keeping information private and confidential reflects respect for persons, beneficence and justice, particularly if the information is sensitive. Since the 1970s, the federal government has issued Certificates of Confidentiality to protect identifiable research information from forced disclosure. Investigators and others who have access to the information are protected from involuntarily disclosing it in administrative, civil, criminal, legislative or other proceedings.

In addition, the Health Insurance Portability and Accountability Act (HIPAA) makes it illegal to reveal defined personal health information.

What is identifiable:

HIPAA defines data elements that make information identifiable. In addition, the increasing collection and use of biospecimens is changing the concept of identifiability of data, particularly when genetic or genomic analyses are done. Research often is multi or interdisciplinary and much social and behavioral research includes collection of biospecimens, for example blood or cells from which DNA is extracted, analyzed and stored. There is concern that such specimens may be anonymized but they are always identifiable and therefore there cannot be an absolute protection of privacy and confidentiality. To accommodate such concerns, it is common practice to share datasets only after data agreements have been negotiated or arrangements are made to use data in data enclaves under supervision and according to strict guidelines. How to assure equitable access to data also is an issue.

6. Research Ethics Committees

Research ethics committees review and oversee research involving humans.
Known as Institutional Review Boards (IRBs) in the US and as Ethics Review Boards (ERBs) or Research Ethics Committees (RECs) in other countries, they are the mechanism for enforcing research ethics standards and overseeing ongoing research. Breaches in accepted ethical practices resulted in the establishment of oversight mechanisms.

Research ethics committees exist is almost every country and operate under legal/regulatory authority. In the US, they are mandated by federal regulations that have the force of law but are appointed by and report to a research institution, such as a university, hospital, or research institute. There also are free standing for profit and not-for-profit IRBs. The Regulations mandate structure, composition/membership, meeting requirements, standard operating procedures and record keeping requirements.

Composition of IRBs/RECs is diverse. Generally, appointments include men and women from various scientific and nonscientific fields, members who are independent of institution(s) conducting the research or the organization(s) sponsoring it, and people who understand the research subjects and their environments. Consultants may be called upon as needed, particularly if the research involves an area in which few or no regular members have expertise. Anyone with conflicts of interest must disclose those interest(s) and not participate in decision-making. Although scientists, advocates, institutional officials and ethicists all have views and interests, it is assumed that the group process, transparency and disclosure will result in balanced decisions.

Level of Review

The U.S. Regulations offer considerable latitude about whether a research proposal requires full review, expedited review or fits one of the exemption categories specified the Regulations. Nonetheless, some institutions are hesitant to use the full range of review options and insist on full committee review of all proposals. Review of research that the ethics committee considers to be minimal risk may be expedited. Some categories of research (46.110), as stipulated in the Regulations, may be exempt. The proposed rule changes will most likely update exempt and expedited categories as well as change the initial review requirements for types of research that may fit them.

6. Research Ethics Committees

In addition to adopting ethical guidelines, IRBs/RECs develop standard operating procedures (SOPS) that that specify how activities are accomplished. For example, they may specify how and when protocols are submitted to the IRB, information they must contain, assess their completeness, describe staff responsibilities and their delegated authorities, specify how and when materials are distributed to reviewers, how and when investigators are informed of review outcome, and other administrative matters. Many research institutions post information about RECs/IRBs on the web along with procedures and requirements for ethics review and approval before research can begin. The IRB Forum provides access to IRB handbooks, guidelines and resources from several institutions. It includes academic IRBs, private non-profit IRBs, and industry IRBs.

The Association of Accreditation of Human Research Protection Programs (AAHRPP) accredits research ethics committees and human protection programs nationally and internationally in an effort to achieve high quality and continuing education.

7. The Global Norm of Ethics Committees

Ideas about what is ethical and how science should be conducted develop and evolve in a social context. Writings about ethical behavior can be traced to Hippocrates but norms developed over the last 60 years were stimulated by the revelations of Nazi medical experiments. Since then, despite the existence of codes of ethics to govern research, several examples of disregard for human welfare have come to public attention. Although many scientists are cognizant of their ethical responsibilities, there have been frank abuses of human participants and many instances of other questionable ethical behavior in research. The revelations of disregard for human welfare in US conducted and supported research resulted in the development of guidance and regulations to prevent abuses and inappropriate research with humans from recurring. Rules were put into place when public opinion prevailed that self-regulation and monitoring by the scientific community is insufficient to protect human research participants. **Examples of these incidents include:**

EXAMPLES
Tuskegee Syphilis Study
The Tuskegee syphilis study examined the natural history of syphilis without informed consent and withheld treatment when it became available. Between 1932-1972, when there was no effective treatment for syphilis, the US Public Health Service supported a study of the natural history of the disease. The research subjects were poor African American males in Macon County, AL. Many of those participating thought they were receiving medical care and did not understand that they were involved in research and were not receiving treatment. The study continued after penicillin was available to treat syphilis. The study was terminated in 1972 after it was publicized by the press and was widely perceived as an abuse of vulnerable subjects (University of Alabama, 2007).
The Willowbrook Study
The Willowbrook study was a study in which parents were coerced to enroll their children in hepatitis research as a condition of entry to an institution for the retarded. Between 1955 and 1971, studies on hepatitis were conducted at The Willowbrook State School, a New York

State institution for the mentally retarded. The facility was overcrowded. Residents were in close physical proximity to one another and experienced repeated respiratory, gastro-intestinal infections and hepatitis. 3-4% of residents and staff had symptoms of active hepatitis infections and/or had blood antibodies and mild liver damage, indicators of previous infections. The research on natural history and prevention of hepatitis involved collecting and filtering virus, feeding or injecting material that contained the virus to children, and administration of gamma globulin. The group that received gamma globulin showed decreased infection. In further research to investigate whether immunity could be induced, Drs. Krugman and Ward identified viruses for Hepatitis A and Hepatitis B, purified antibody-containing blood from affected patients and injected it into newly arriving children to see if the disease would be prevented. They found that subjects who received the injections made antibodies that protected them from infection. Parental consent was given before children were infected. Those being studied were isolated so they would not infect other children. The investigators posited that potential benefits of a vaccine outweighed the risks to the children. Others posited that the letter presented to parents for consent minimized the fact that their children would be infected deliberately. There was a waiting list for admission to the institution and it was alleged that those who consented to participate in the research were admitted while those who did not consent were made to wait. This implies that parents may have been coerced to give consent to participate in research to obtain admission to the institution and care for their children.

The Jewish Chronic Disease Hospital Study

The Jewish Chronic Disease Hospital study of immune response was a study in which cancer cells were injected into chronically ill and/or demented elderly persons without their consent.

In 1963 research was conducted at the Jewish Chronic Disease Hospital in New York City to study the immune system and transplant rejection process. Chronically ill patients, some of whom were demented, who did not have cancer were injected with live human cancer cells without consent. The investigators claimed they did not inform the patients or get their consent because they did not want to frighten them and because they believed that the patients would reject the cells. An investigation found that the study had not been presented to the hospital's research committee and that the doctors caring for the patients were not consulted about the study The investigators were found guilty of fraud, deceit and

unprofessional conduct.

The New Zealand National Women's Hospital Study

The New Zealand National Women's Hospital study of cervical carcinoma in situ was a study in which non-consenting women with in situ and invasive cancer were observed but not offered available treatment options.

In 1966 a study of the natural history of cervical carcinoma in situ was initiated at New Zealand National Women's Hospital. The study continued for more than 20 years. The investigator believed that some portion of cervical smears and biopsies are abnormal but do not develop into invasive cancer. The women underwent screening, and repeated cone and punch biopsies but did not receive treatment, even after in situ and/or invasive cancer was detected. When invasive cancer was found, women were reclassified as having entered the study with cervical cancer, i.e. the initial screening tests missed the diagnosis. During the first 3 years of the study, some cancers became invasive but treatment was not offered in all cases and the study continued. Women were not informed of treatment options and many did not consent to research or know they were participating in research. The investigator, who believed that some females are born with cervical cell abnormalities, screened more than 2,000 infants at birth without parental knowledge or consent. The study was reported by the lay media in 1988. A full inquiry was done that resulted in changes in New Zealand laws about practice and research. Among the findings were that the study underwent no scientific review and the research ethics committee consisted of internal staff except for one member; the ethics committee had no written principles or guidance; consent forms were rarely included with research proposals; the department head chaired all meetings and most proposals were from his department, including some on which he was principal investigator. As a result of the inquiry, the ethics committee was disbanded and the Aukland Hospital Board under the Director General of Health was charged with creating independent committees that would follow specific procedures. Provisions governing research with humans in New Zealand were revised, as were policies for patients' rights. A settlement was reached with compensation for the research participants (Women's Health Action Trust, 1988).

The Guatemalan Study

The Guatemalan study infected non-consenting subjects with sexually transmitted

diseases. (University of Alabama, 2007; U.S. Department of Health & Human Services, 2011) Susan Reverby was conducting research on the Tuskegee study. While searching through archived material, she discovered a second study on syphilis and other sexually transmitted diseases conducted in Guatemala between 1946-48. In this study, conducted by one of the Tuskegee investigators and also supported by the US Public Health Service, men and women engaged in sexual relations with infected partners or were inoculated with syphilis and then treated with penicillin. Following its disclosure, the secretaries of the U.S. Department of State and Department of Health and Human Services apologized. In addition, the Presidential Commission for the Study of Bioethical Issues has been asked to review US human protection programs (Reverby, 2011; U.S. Department of Health & Human Services, 2011)

7. The Global Norm of Ethics Committees

Government authorized ethics committees, because of their diverse membership from and outside the institution, are seen as being more free of bias and conflicts of interest than an internal institutional group, the investigators themselves or a committee composed entirely of scientists. Although under the aegis of an institution or government that is not devoid of interests, the ethics committee model has been adopted worldwide as the best choice that is available and practical.

The ethical principles that are part of the US Regulations are applied by investigators in design and conduct of research. They also are applied by the IRB and scientific review group in their assessment of the scientific importance, soundness and suitability of the research.

Ethical guidelines/codes stipulate that research involving humans should be subject to prior ethical review to ensure that:

- **Ethical guidelines are followed;**
- **Research is scientifically valid;**
- **Risks of harm are minimized to extent possible;**
- **Potential benefits outweigh risks of harms;**
- **Selection and recruitment are fair;**
- **Research participants (or their representatives) provide voluntary informed consent; and**
- **Research fosters health, human rights, care of participants and/or their communities.**

Exercise 3

Listed below are several examples of research cited for ethical violations. Click on the specific violation(s) and the ethical principle(s) violated in that example.

A. Tuskegee, 1932-1972

Specific Violations:	Principles Violated:
Lack of informed consent	Respect for persons
Failure to minimize risks and maximize benefits	Beneficence
Withholding of treatment	
Lack of proper review by an ethics committee	
Lack of protections for a vulnerable population	

How did I do?

B. New Zealand, 1966-1988

Specific Violations:	Principles Violated:
Lack of informed consent	Respect for persons
Failure to minimize risks and maximize benefits	Beneficence
Withholding of treatment	
Lack of proper review by an ethics committee	
Lack of protections for a vulnerable population	

How did I do?

C. Jewish Chronic Disease Hospital, 1963

Specific Violations:	Principles Violated:
Lack of informed consent	Respect for persons
Failure to minimize risks and maximize benefits	Beneficence
Withholding of treatment	
Lack of proper review by an ethics committee	
Lack of protections for a vulnerable population	

How did I do?

D. Guatemala, 1946-1948

Specific Violations:	Principles Violated:
Lack of informed consent	Respect for persons
Failure to minimize risks and maximize benefits	Beneficence
Withholding of treatment	
Lack of proper review by an ethics committee	
Lack of protections for a vulnerable population	

How did I do?

8. Current Issues Concerning Ethics Committees

Alternate IRB Models

U.S. IRBs were designed as institutional committees that would be familiar with local socio-cultural values. In many countries, such committees are based in health ministries and are national in scope. Today it is common for research to span many communities and even countries. Ethics committees from different institutions and/or geographic regions may not agree. Negotiating acceptable human protections becomes a cumbersome, lengthy and costly process. To facilitate research and resolve conflicts among local IRBs, central IRBs have been proposed for collaborative multi-site studies. Central IRBs may be ongoing or study specific, composed of members from a sample of the sites involved in research or may be totally independent and free-standing. The US experience is that many institutions are reluctant to relinquish their autonomy and responsibilities to a central IRB. Institutions also are concerned about compliance with regulations, local rules and policies and about liability. In the U.S., although models such as free-standing for-profit and not-for-profit committees for human research protection in research exist, to date, the institutional ethics review committee is the most prevalent (Association of American Medical Colleges, 2011).

Breadth and competence of ethics committees:

IRB or ethics committee review may vary as a function of the type of research to be reviewed. Some committees review studies in one or two disciplines while others may review the entire range of human studies carried out in their institution. Ethics Committees should be familiar with the different types of research methods and the ethical issues related to methods and projects they review. Some types of research commonly have method-specific ethical issues. For example, when the research demands that full information cannot be disclosed without compromising the research, the informed consent process must be modified if the research is to proceed as designed and plans for debriefing at the conclusion of the study must be assessed.

Some behavioral and social scientists maintain that the Belmont Principles were developed in the context of biomedical research and that they are not readily applicable to behavioral/social research. More specifically, the objection voiced is that many IRBs lack adequate competence to review behavioral/social research. Although behavioral/social research often is minimal risk, the probability and level of risk needs to be assessed.

8. Current Issues Concerning Ethics Committees

Community Representation and Engagement

Some think that we need new human protections models that incorporate deliberate community engagement. Community representatives on scientific and ethics review committees may feel intimidated by the other members. Use of research materials may change over time. Would robust community advisory boards that oversee data repositories and biobanks add protections and improve human welfare?

Scope / Applicability of the Regulations

The U.S. Regulations for protection of human subjects apply only to federally supported or conducted research. Most research in this country is not federally supported. Therefore, there is a large amount of research activity that is not required to comply with the Federal Regulations. Many organizations have elected to comply and even to become accredited by the AAHRP, but not all. Several Congresses have introduced legislation to extend the scope of human protections to all research but to date the legislation has not passed.

8. Current Issues Concerning Ethics Committees

Mission Creep

IRBs were established to protect human subjects in research. Some committees review the quality of the science as part of their mission. There is debate about whether this is appropriate.

> **Research that is not sound scientifically is unlikely to result in trustworthy findings. Therefore, such research may be a disservice to public health, policy and general knowledge, and to future studies that are based on its outcomes.**

Research that is scientifically unsound also reflects a lack of respect for participants whose time is wasted, for animals and for other research resources, including research staff. However, there is disagreement within the scientific community about whether IRBs should engage in scientific review. Some argue that institutional scientific review and/or study section review are sufficient. Others argue that if scientific flaws are noted, they should be addressed as a condition of IRB approval. Moreover, in some settings and in the developing world, there may be no scientific review other than that provided by the research ethics committee.

The Illinois White Paper (2007), identified many concerns about IRBs and the extent to which they fulfill their mission. They argue that some types of research should not require IRB review, that The Belmont Report definitions of research, minimal risk and benefit are vague and limited, that the IRB system has become bogged down in procedural matters, that empirical research on IRBs is lacking, and that changes are in order.

8. Current Issues Concerning Ethics Committees

Conflict of Interest

Some claim that institutional committees have an inherent conflict of interest because external research funds that benefit the institution are contingent on IRB approval of the research. Review by free-standing committees to avoid this conflict is an alternative but is much less commonly used in the U.S., especially if the free-standing committee is a for-profit organization. Aside from institutional conflicts of interest, investigators may have individual financial conflicts of interest, personal conflicts of interest, and professional conflicts of interest that may affect their behavior as reviewers of manuscripts and funding applications. IRBs may be assigned the task of identifying and managing conflicts, especially financial conflicts of interest, in addition to their other responsibilities.

Cost and Burden

There is general agreement that the U.S. ethics review system is expensive, weighed down by procedural requirements, and time-consuming for all involved. Yet, we do not know how well human participants are protected or how consistent that protection is across institutions and research projects. Some good research on this issue would be a major contribution.

The proposed changes to the Common Rule address many of these issues. A table summarizing the proposed changes and the rationale underlying them has been prepared by OHRP (U.S. Department of Health & Human Services, 2011).

Exercise 4

For each of the following scenarios, identify which evolving ethics issue should be considered.

Scenario 1 of 7:

Research on diabetes prevention plans to recruit from four Native American tribal groups. Informed consent is sought from each potential participant. The investigators are surprised when participants report they cannot consent to research without consent of the tribe following review and approval by a tribal committee.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 2 of 7:

An IRB is reviewing a study on the impact of parent's imprisonment on 10-13 year old children. The composition of the IRB is: 4 MDs in the areas of infectious diseases, psychiatry, oncology, and hematology; 3 behavioral/social scientists in psychology, sociology, and research methods; 4 non-scientists including 1 ethicist, 1 lawyer, 1 member of the clergy, and 1 executive director of an advocacy organization. A member moves to defer the review pending input from 1 or more pediatricians and child psychologists.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 3 of 7:

A study of breast cancer screening is being done. To increase recruitment in the Hispanic community, the investigators hold community meetings to publicize their study. They invite comments on community concerns and solicit suggestions on how to encourage participation and on appropriate incentives.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 4 of 7:

University researchers receive industry support to conduct a clinical trial. The researchers are unsure of whether or not their research must be reviewed by the university IRB.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 5 of 7:

An IRB discusses serious flaws in the research design and analytic plan. The proposal is returned for amendment of scientific weaknesses. The investigators are furious that the IRB has reviewed the science as well as the ethics, claiming it is out of the committee's scope of responsibilities.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 6 of 7:

An investigative team has developed a vaccine for a tropical disease and has successfully completed animal studies and safety and efficacy studies in humans. The vaccine is to be tested in a tropical developing country with a poor health services delivery system. The clinical trial is a randomized design. It does not include a provision to vaccinate the larger population or members of the control group at the end of the trial. The investigators say that there is no adequate public health delivery system to vaccinate the larger population.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

Scenario 7 of 7:

An audit of study records done as part of a continuing review reveals discrepancies in the dates some subjects were tested and the dates on the signed consent forms. On closer examination, it appears that the participant's signatures, from the handwriting, appear to be those of a single individual. A research assistant, when questioned, admits to having forged signatures and dates.

- **Breadth and competence of committees**
- **Community involvement**
- **International research**
- **Federally or non-federally funded research**
- **Sociocultural differences**
- **Mission creep**
- **Scientific misconduct**

9. Scientific Integrity

No matter how good the system to protect human, animal and environmental welfare and encourage ethical behavior, the actual conduct of research cannot be monitored all of the time. Investigators and their research teams need to be trusted to behave appropriately. There are bound to be breaches, some intentional and frank misconduct and others the outcome of sloppy practices, poor supervision and/or error. Unethical practices led to the establishment of research ethics commissions and the regulations that have the force of law to govern research. Concerns about scientific misconduct resulted in the establishment of a federal Office of Research Integrity (ORI) as well as policies to encourage ethical research and other responsible conduct. The Office of Research Integrity engages in education, research, and investigations as well as imposes sanctions for scientific misconduct. The definition of scientific misconduct and the U.S. federal policy governing it is available at the Office of Research Integrity and at the Federal Register.

Of the allegations made to the Office of Research Integrity, about 2% result in findings of scientific misconduct, i.e. fabrication, falsification or plagiarism. Misbehavior that does not fit the definition of scientific misconduct is more frequent. In a meta-analysis, Fanelli, 2009 reported that up to 72% of respondents report that they have direct knowledge of questionable research practices.

Example 7

Example A:

A professor working on cardiac function and aging is hoping to develop a new drug. He asks a colleague who works for industry to share some data from related work. The colleague is willing to share his data but asks that it be kept confidential and not shared with others. The data, when it arrives, is stamped “confidential – Pre-IND” and the request for confidentiality is repeated in a cover letter. The professor submits a grant application. During scientific review, a reviewer alleges that the preliminary work section of the application contains data that were obtained in another lab without that investigator’s knowledge or permission. The principal investigator on the grant application represented another scientist’s work as his own. The review administrator suggests that review of the application be deferred and says that she will contact the Office of Research Integrity. Assuming the allegation is found to have substance and merit in an inquiry and

investigation, what is the ethical breach(es) in this case?
(Scientific misconduct – plagiarism and falsification of research experience by presenting another's work as his own).

Example B:
A trainee on a training grant contacts the funding agency and claims that he is being paid less than the stipend requested and approved for trainees.The funding agency contacts the institution, requests financial records and progress reports, and prepares to conduct an audit. The agency finds that there are trainees listed for whom there is no documentation of appointment, that some progress reports involve trainees who do not meet funding agency eligibility requirements, that some progress reports duplicate those from prior years, and that financial records do not correspond to appointments or to projects. What is the ethical breach in this case. (Financial mismanagement. This is not scientific misconduct according to US federal definition but is not responsible conduct. However, falsification might also be involved here. The researcher has hired trainees who are ineligible because of policy and/or legal requirements of the funding agency. The researcher, in signing the application, has assured compliance with all requirements, a false assurance.)

Example C:
A researcher in molecular mechanisms of diabetes publishes a paper that attracts the attention of a biotech company. A senior scientist from the company meets with the researcher. The company scientist proposes that they develop a collaborative relationship and offers additional support for the research, including two technicians, for three years. The offer is attractive to the researcher. A week later the researcher receives a collaborative research agreement. It documents the offer and also contains other provisions. One is that the researcher and company scientists will co-author all papers, that the company must have access to all data, that company statisticians will conduct the analyses and that company officials will approve all publications prior to submission. What is the ethical issue(s)? What should the researcher do? (The issue here is conflict of interest. The researcher should decline the proposed arrangements if s/he is unable to negotiate an alternative arrangement.)

Example D:

A junior faculty member submits a manuscript for publication of federally-supported work she completed as a postdoctoral fellow at another institution. The journal editor, in reviewing the manuscript, suspected that several figures in the manuscript were manipulated. The editor notified ORI. ORI, in turn, notified the institution where the work was done and that institution began an inquiry that led to an investigation. The author, as a graduate student and postdoctoral fellow, was found to have manipulated or falsified more than 20 images, reused control data and reported inaccurate data in progress reports and grant applications.

- Did the junior faculty member commit scientific misconduct?
- What actions should be taken as a result of the behavior?
- What other issues does this case raise?

(This is an example of scientific misconduct – data falsification and fabrication. Retractions of published papers is appropriate. Societies at which presentations were made should be notified. This case raises the issue of adequacy of supervision and mentorship. If an editor spotted the manipulation of data, it is highly likely the mentor would have noticed if s/he had reviewed the primary data and the manuscripts. Perhaps new policies about supervision and mentoring need to be implemented by this institution.)

Exercise 5

Decide whether each of the following statements about Research Ethics Committees is true or false.

In the US, it is mandatory that all institutions conducting human subjects research have an Institutional Review Board.

True | False

IRB review and monitoring of research are deemed necessary because guidelines and regulations are insufficient to prevent unethical behavior.

True | False

Research misconduct involves falsification, fabrication, plagiarism, and financial dishonesty.

True | False

9. Scientific Integrity

Responsible science requires integrity with respect to:

- Ethical principles and behavior;
- Intellectual input;
- Data collection, management, retention, analyses, reporting, sharing and ownership;
- Use of resources (equipment, time, training and supervision);
- Respecting human/animal subjects, colleagues and collaborators;
- Publication and authorship practices;
- Reviewing and editing;
- Disclosing interests, avoiding or managing conflicts of interest; and
- Teaching, mentoring and supervising.

Scientific Integrity, Honesty, and Respect for Persons

Research design and methods need to be appropriate to the topics studied and to the hypotheses being tested. If not, the research is a waste of time and resources, disrespectful to subjects, staff and the scientific enterprise. Careful preparation of the research plan and peer review help assure that the results will be scientifically valid and reliable. Data acquisition needs to be methodologically appropriate, transparent, be carried out by well-trained and supervised data collectors and only after all required approvals have been obtained. Plans for data retention must be detailed, and for research involving humans, the consent process must make clear whether the data will be retained, how and for how long, whether it will be kept with identifiers or not, and how confidentiality will be protected. Who will have access during and after the research and who owns the data needs to be made clear during the consent process. Analyses must be scientifically valid and appropriate to what participants consented to.

9. Scientific Integrity

Example 8

The Havasupi Indian tribe was disturbed about an increase in diabetes among tribe members. In 1989 the tribe agreed to participate in research to explore whether a genetic cause for the increase could be found. As part of the research, blood samples were taken and stored. Two years later, negative findings were published. The Havasupi were not aware that use of the samples continued for two decades for research on migration, schizophrenia and other topics. A lawsuit claimed that research was done that went against tribal cultural beliefs and teachings and the consent to use blood samples for analyses was for the diabetes research only. The geneticist claimed to have obtained permission to conduct other studies. The tribe prevailed, was awarded compensation, and the university was ordered to return the samples to the tribe. The case raises questions about the honesty of the researchers and whether the researchers took advantage of a vulnerable group. The tribal member who brought the lawsuit said: *"I'm not against scientific research, I just want it to be done right. They used our blood for all these studies, people got degrees and grants, and they never asked our permission."* (Harmon, 2010). This example describes a human subjects consent problem and also a perceived lack of integrity of the scientists.

Example 9

A junior scientist works with his group to prepare a grant application on which his boss is the Principal Investigator (PI). The application is funded. The junior scientist is shocked when his boss informs him that there is no role for him in the research and that he will not be supported by the grant. He alleges that the application show-cased his ideas, methodological innovations and prior discoveries in the preliminary research section. He maintains that the application would not have been funded without his substantive contributions and alleges plagiarism on the part of the Principal Investigator. Is there substance to this allegation of scientific misconduct? (This junior scientist does not know that contributing to the preparation of a grant application does not obligate the Principal Investigator to support any or all the contributors. Whether or not there is plagiarism depends on whether the PI is found to present the work of others as his own or gives appropriate attribution and citations. There does seem to be a communications failure between the PI and junior scientists.)

9. Scientific Integrity

Authorship

The most frequent allegations of unethical behavior received by federal officials involve authorship. In some disciplines it is customary for senior investigators who run labs or departments but who have had little to do with the conduct of the research, to be listed as first or last author. In other disciplines, such as psychology, that is considered unethical. Honorary authorship is not appropriate. Criteria for authorship are defined by disciplinary codes of ethics and by journals and require a substantive intellectual input to the research. Some journals, e.g. Science, require that authors specify their contribution and verify that they have read the paper and reviewed the data, that the report is accurate and that any and all interests are disclosed (Science, 2011; International Committee of Medical Journal Editors, 2009; American Psychological Association, 2011).

Example 10

A doctoral student has completed her research and has written four manuscripts that she plans to submit to a top journal. She has acknowledged help from her advisor and research staff. She shares the manuscript with her mentor and department chair. Her mentor applauds the work, considers it important, and informs her that the department chair and he will co-author the papers. The student is appalled because the department chair has made no contribution to research. Her mentor provided guidance but did not contribute to the main ideas or methods. He did make facilities and equipment available and read earlier drafts of the papers. The student is concerned that if she does not acquiesce, her degree may be in jeopardy. If she does agree to co-authorship, she feels that she being unethical.

What should she do?

Issues surrounding authorship, acknowledgments, publication policies, disclosure of bias and interests and handling misconduct allegations are common to all kinds of research, regardless of methodology or content. When research involves large teams, publication committees with clear policies about these topics are the norm. Whatever the arrangements, they should be spelled out in advance and procedures to resolve conflicts need to be in place. Best practices can be identified by consulting institutional policies, professional societies' ethical codes, and the uniform guidelines of the International Committee of Medical Journal Editors Investigators should agree early in their research planning who does what and who will be authors.

9. Scientific Integrity

Peer Review

Contributing to the scientific enterprise by serving on advisory committees when invited and, as a peer reviewer for research applications and publications is a civic obligation of scientists. In such roles it is critical to be intellectually honest, allocate adequate time and energy to the task, maintain confidentiality and avoid real or apparent conflicts of interest. The quality of science is dependent on good quality peer review. Participating in that process is an important professional activity.

Example 11

A scientific review group is discussing a grant application. One of the reviewers mentions that since the application is not in his area, he sought advice from a colleague, and then read his review. The chair of the review group points out that confidentiality has been violated and proposes that the committee defer the application for re-review. *Do you agree with the chair's suggestion?*

9. Scientific Integrity

Mentoring and Supervising

Mentoring and supervising colleagues and students in science and ethics are important to creating a culture of ethical conduct and scientific integrity. Policies and rules governing research are not intuitive and must be taught. Standard operating procedures need to be explained so that staff knows what to do and why it is important to adhere to the study protocol. The scientific community is diverse and we cannot assume common culture, values and experiences. Different cultures have different behavioral expectations. To ensure that research meets our ethical and technical standards, we must be explicit about what those standards are. When problems come up or when questionable practices occur, we must teach research staff and participants to discuss them rather than hide them. A good mentor and research leader will be familiar with research procedures, will review the raw data and analyses, and address deviations that impact the research at regular team meetings, before there are major ethical breaches and before they affect the body of scientific literature. This requires trust and the expectation that there will not be reprisal for acknowledging errors, misbehavior and other problems.

Example 12

A laboratory doing cutting edge research in a competitive area is alleged to have published falsified data. During an inquiry several lab members are interviewed. A scientist trained in another country tells the interviewer that part of her responsibilities as a researcher is to confirm the hypotheses of the senior scientist, even If doing so means manipulating some images. The junior scientist explains her career and future employment are dependent on the senior scientist.

9. Scientific Integrity

Reporting Misbehavior and Suspected Misconduct

Reporting observed or suspected misbehavior is a sensitive issue. Although there is an ethical obligation to report questionable behavior and scientific misconduct, there is rarely a good outcome for the accused or accuser. The person who reports a problem may be considered a troublemaker, may suffer reprisal, and may become ostracized in the work environment. Yet, failing to report can result in dissemination of false results on which therapies, future research, and/or policies may be based. It also undermines trust in science and science itself.

Example 13

A postdoctoral fellow comes into the office during the weekend to pick up something she forgot. She is surprised to see another postdoctoral fellow busy at work, apparently doing data analyses. They chat briefly and the postdoc explains he is there when things are quiet because he wants to finish a couple of papers and submit them to journals. She thinks nothing of the interaction but then realizes that she can't recall what papers the postdoc was talking about. She cannot identify studies that are close to ready for publication. That week, at lab meeting, she asks the postdoc to discuss the papers he is finishing up. Others in the group look surprised and say they did not know he was ready to submit manuscripts. When the postdoc began talking about the papers, others said that they had not seen the data analyses and asked to see them. The results looked terrific – more supportive of the hypotheses than earlier analyses. The postdoc begins to wonder whether something fishy is going on. She discusses her concerns with her colleague later that afternoon. He vigorously denies any wrongdoing. She reviews the data and becomes more concerned. *What should she do?*

9. Scientific Integrity

Research Management

Few scientists are trained in management, yet good stewardship is critical to sound outcomes, particularly when engaged in collaborative and/or multi-institutional cross-disciplinary investigations. It is important for all investigators and their teams to understand what is expected of them in all stages of the research.

Collaborative research is well served by written agreements that specify who has lead responsibility for:

- **study structure**
- **each research aim or area**
- **ethical and safety requirements**
- **allocation**
- **training and supervision of personnel**
- **disclosure and management of conflicting interests**
- **resolution of intellectual property and inter-personal disputes**
- **who owns, has access to and maintains equipment**
- **ways in which data will be shared and managed including depositing data to a central point for cleaning and analysis**
- **ways in which publications will be prioritized and how authorship will be determined**

Plans for submitting research reports and for orderly termination of research also need to be negotiated. These all are skills that benefit from training, supervision and experience. Conducting research ethically and with the highest integrity requires forethought, ongoing monitoring and supervision.

10. Summary

Ethical principles or norms are guides to help us behave in ways that are morally right. They may be useful in helping us to balance competing values and to analyze ethical dilemmas. Ethical principles outlined in this chapter may be interpreted and applied in different ways as a function of individual and societal experiences and values. At times, even after careful consideration and ethical analysis, the best course of action is not clear. In such situations, you may seek consultation and then rely on your best judgment.

Education about ethics of research and scientific integrity, by reading case analyses and by setting an example, may foster valid and reliable research. Ethical behavior of scientists is important to public trust and to our body of knowledge.

Scientists share the responsibility to:

- communicate that their own and other institutions value responsible conduct of research;
- act on their own values, sense of responsibility, and moral integrity;
- teach research ethics and responsible conduct;
- uphold the policies and procedures for responsible science spelled out by government, professional/scientific societies, journals and institutions; and
- encourage the report of inappropriate behavior and schedule continuing discussions of ethical issues and responsible conduct of research.

11. Resources

Further Reading

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Selected Web Resources

Resnick, D. B. What is Ethics in Research and Why is it Important?
This article is an easy introduction to research ethics.
http://www.niehs.nih.gov/research/resources/bioethics/whatis.cfm

The Office for Human Research Protections site includes national and international guidelines and regulations, educational written materials and videos, archived resources, and notices of educational programs.

http://www.hhs.gov/ohrp/index.html

The National Institutes of Health site Bioethics Resources on the Web includes links to federal and non-federal resources and links to selected topics. The site also includes links to ethics tutorials, case studies and ethics-related organizations.
http://bioethics.od.nih.gov/index.html

The Office of Research Integrity site includes federal policies and regulagtions, publications, educational material including a video on avoiding misconduct. It also includes information on handling suspected misconduct.
http://ori.hhs.gov/

IRB handbooks and guidelines: Google IRB Handbook or IRB Guidelines or go to an institution's home page and search within it for Protection of Human Subjects or IRB.

Federal Regulations
http://www.regulations.gov/

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13. Author Biography

Miriam Kelty consults on research ethics, scientific integrity and research strategy. Her doctoral training at Rutgers University was interdisciplinary in psychology, psychobiology and animal behavior. For 20 years Dr. Kelty was Associate Director of the National Institute on Aging, U.S. National Institutes of Health (NIH) and Director of Extramural Activities.

Dr. Kelty is a leader in the ethics of research. After participating in the development and publication of Ethical Principles for the Conduct of Psychological Research with Human Participants by the American Psychological Association, she joined the staff of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This group produced more than a dozen studies, including the Belmont Report, which has been the basis of human research protections in the U.S. and abroad.

At NIH Dr. Kelty started the Inter-Institute Bioethics Interest Group, a forum for discussion of emerging and ongoing ethical issues in research. Dr. Kelty developed Bioethics Resources on the Web to disseminate resources and teaching materials. As a consultant she continues to advise NIH and other organizations on ethical issues in research such as consent processes, biorepositories and use of stored samples, international research and recruitment and retention of clinical trial participants. Her leadership and her contributions to research ethics have been recognized by the U.S. Department of Health and Human Service, NIH, academic and association awards.

She is active in scientific and professional organizations, is a fellow of the American Association for the Advancement of Science, the American Psychological Association, the American Psychological Society and the Gerontological Society of America. She is a mentor for NIH scientists and for members of Public Responsibility in Medicine and Research. She recently completed terms on the program committee for the AAAS and on the peer review and policy committee for the Canadian Institute of Health Research. Currently Dr. Kelty serves on the Institutional Review Board for the Uniformed Services University of the Health Sciences, the ethics committee for the CTSAs, the Human Research Committee for the American Psychological Association. In addition to NIH, she consults with WHO and World Bank.