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
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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.