Research Ethics Training Curriculum

FHI Training

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Authors:

Roberto Rivera
David Borasky
Robert Rice
Florence Carayon

FAMILY HEALTH INTERNATIONAL

CREDITS

Authors:

Roberto Rivera, MD, Director—Office of International Research Ethics (OIRE), FHI
David Borasky, BA, Associate Director—Office of International Research Ethics (OIRE), FHI
Robert Rice, MA, Deputy Director—Field, Information and Training Services (FITS), FHI
Florence Carayon, MA, Bilingual Health Training Officer—Field, Information and Training Services (FITS), FHI

Case Study Writers:

Paul Feldblum, MPH, PhD; Ron Roddy, PA, MPH; Kelley Ryan, BA; Julia Welch, MS; John Stanback, MA, PhD; Cindy Waszak, MA, PhD; Theresa Hatzell, MPH, PhD; Hally Mahler, MA, MPH; David Borasky, BA.

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Introduction to the Research Ethics Training Curriculum

It is essential that fundamental ethical principles be included in the design and implementation of research involving human participants.

Ethical research principles are considered universal, transcending geographic, cultural, economic, legal and political boundaries.

Although these principles are universal, the availability of the resources needed to maintain these principles is not universal, and the procedures used for the ethical vigilance of research studies may not be optimal. For instance, no universal principle exists to monitor how research will be conducted.

Regardless of limitations, ethical research principles must guide those who plan, conduct and sponsor research that involves human participants. Human participation in research projects has contributed to better quality of life through the development of diagnostic tools and successful treatments.

This *Research Ethics Training Curriculum* has been developed for international researchers who:

- conduct research that includes human participants
- want to incorporate fundamental ethical considerations in design and implementation of their research

The Lotus Flower

The *Research Ethics Training Curriculum* uses the **lotus flower** to symbolize fundamental ethical elements. The lotus flower image represents **purity and perfection** in some cultures. The ethical considerations discussed in this curriculum aim for a pure and perfect research design—the foundation on which ethical research study is developed and implemented.

However, each research design will be unique in that it will be:

- specific to the study's design and research outcomes
- important to the local research population
- intrinsic to the local culture

Because each research design will be unique, a different lotus flower—representing the local culture and characteristics of each research study—is shown at the beginning of each chapter of the *Contents* section of the *Research Ethics Training Curriculum*.

The *Research Ethics Training Curriculum* offers international researchers:

- an overview to the development and philosophy of research ethics
- case studies so that the learner can consider real-world examples of ethical issues
- materials to assist researchers in designing studies that respect local regulations, cultures and expectations
- ancillary reference documents on modern perspectives that shape the research ethics field

The researcher sets as a primary goal the protection of research volunteers while at the same time incorporating ethical considerations for project design and implementation.

The principles of research ethics have grown out of abuses in the past. Today a great amount of attention is directed at research that involves human participants. International research ethics ensure that research conducted at the local level follows international expectations and standards. Following such international expectations validates the time and energy invested by the researcher—as well as the good will and trust invested by the participants.

It is essential that local researchers familiarize themselves with the subject matter in this curriculum. Knowing current attitudes about research ethics will assist each researcher in aiming for the goal symbolized by the lotus flower—purity and perfection in each research study.

How to Use This Curriculum

This *Research Ethics Training Curriculum* is designed to engage the learner. Adult learning and retention improves when the learner participates actively in the learning process. The *Research Ethics Training Curriculum* can be used as either an interactive

self-study program or as a participatory, group training experience. It is expected that completing this curriculum will take approximately 4 hours.

The curriculum is divided into 5 sections:

- *Contents*
- *Case Studies*
- *Evaluations*
- *Slide Masters*
- *References*

The *Contents* section is composed of copies of color summary slides followed by narrative text. At times, the narrative is followed by a shaded box labeled "Learner Note." Learner notes contain interactive questions or activities. Write down your ideas in the shaded learner note box. If you are facilitating a group training experience, ask the group to call out or write on flip chart paper some answers to the questions asked by the learner notes. This will help the users of the curriculum retain the key messages.

The *Case Studies* section provides 8 reproductive health case studies followed by thought-provoking questions. The case studies help anchor the curriculum to the reality of designing and implementing research studies. These case studies address reproductive health ethical considerations and are based on actual situations encountered by researchers at Family Health International.

Five of these case studies are found in the *Contents* section of the curriculum; the other 3 case studies are found only in the *Case Studies* section. (If you are facilitating a small group learning experience, you will want to photocopy the case studies for your participants to have available during the training session.) The reader will find some of the possible answers to the case studies on page 10 of the *Case Studies* section.

The *Evaluations* section includes a pre-test, a post-test, an answer key to the pre and post-test and a curriculum evaluation form. If you are interested in receiving a certificate of completion from FHI, you will need to return the Reader's Evaluation form (given at the end of the *Evaluations* section) to FHI, as noted below.

The *Slide Masters* section contains full-sized copies of the summary slides from the *Contents* section. If you are facilitating a group training experience, make transparencies for use on an overhead projector.

The *References* section includes text of the *45CFR46 (Public Welfare and the Protection of Human Subjects of the U.S. Code of Federal Regulations; the 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects*; *Operational Guidelines for Ethics Committees That Review Biomedical Research*; *The Belmont Report*; *The World Medical Association Declaration of Helsinki*; various Internet references; and a suggested bibliography.

Getting Started

This curriculum is designed for either the individual self-learner or the facilitator of a group learning experience.

If you are presenting this material to a group, you will need to:

- Look over the enclosed materials to prepare for the group training.
- Identify and reserve a centrally located meeting room that is suitable for the group size and for viewing overhead transparencies. Communicate meeting location and time to participants.
- Rent or locate an overhead projector and projection screen or a computer projector (if using the CD-ROM) to be used for the presentation.
- Rehearse your presentation, preferably in the room and using the equipment you plan to use during the actual presentation.
- Gather other supplies including blank paper, pens, nametags, pens suitable for writing on overhead transparencies, flip chart and markers, etc.
- Make sure there are copies of the case studies, note-taking handouts, pre-tests and evaluations for each participant.
- Greet the participants as they arrive at the meeting site. Use name tags if participants do not know each other. Ask them to briefly introduce themselves.
- Introduce the presentation by telling participants that these materials are developed by Family Health International. The *Research Ethics Training Curriculum* is targeted for biomedical and social science researchers with formal education in their respective areas of scientific interest.
- Tell participants that a certificate of completion for the training can be requested from Family Health International (see below).
- Pass out audience note-taking handouts, reader's evaluation and presenter evaluation forms. Encourage the participants to make comments and suggestions on any of these forms during the presentation.
- Administer the pre-test.
- Begin the curriculum presentation; try to follow the suggested schedule.
- Take a refreshment break.
- Complete the curriculum presentation.
- Facilitate discussion of the presentation, including both general comments and specific comments about the slides, narrative, case studies, pre-test, etc.
- Complete and collect the Reader Evaluation form. Send the Reader Evaluation form to FHI (see contact information, below).

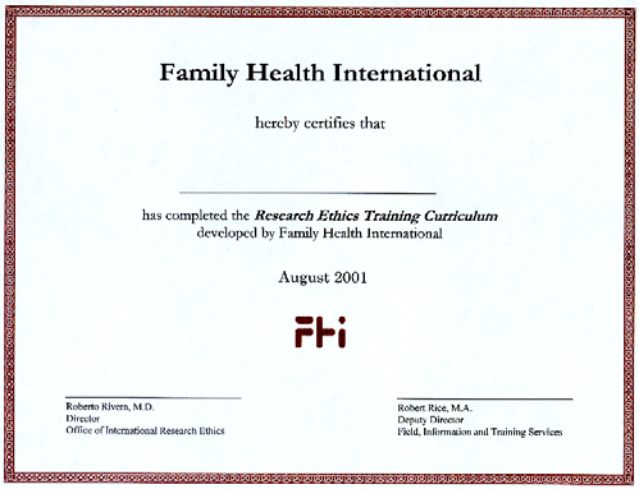
If you are an individual self-learner:

After you read this introduction section but before you begin reading the *Contents* section, take the pre-test found in the *Evaluations* section. Taking the pre-test will alert you to important information in the *Research Ethics Training Curriculum*. After you take the pre-test, continue with the curriculum, beginning at the *Contents* section.

When you have completed all of the material in this curriculum—approximately 4 hours of time—take the post-test found in the *Evaluation* section.

Certificate of Completion

FHI's Office for International Research Ethics (OIRE) will send a certificate of completion after the *Research Ethics Training Curriculum* is completed.



Family Health International

hereby certifies that

has completed the ***Research Ethics Training Curriculum***
developed by Family Health International

August 2001

FHI

Roberto Rivera, M.D.
Director
Office of International Research Ethics

Robert Rice, M.A.
Deputy Director
Field, Information and Training Services

Send your **completed Reader's Evaluation** (found in the *Evaluations* section) to:

Office of International Research Ethics
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
USA

Make sure to enclose your correct mailing address or a business card so that FHI can mail your certificate of completion. *Make sure that your mailing address is complete—include the name of your country!*

Contact Information

Feel free to contact FHI at the mailing address above, visit our Web site at www.fhi.org, or e-mail us at ethics@fhi.org

We look forward to hearing from you!

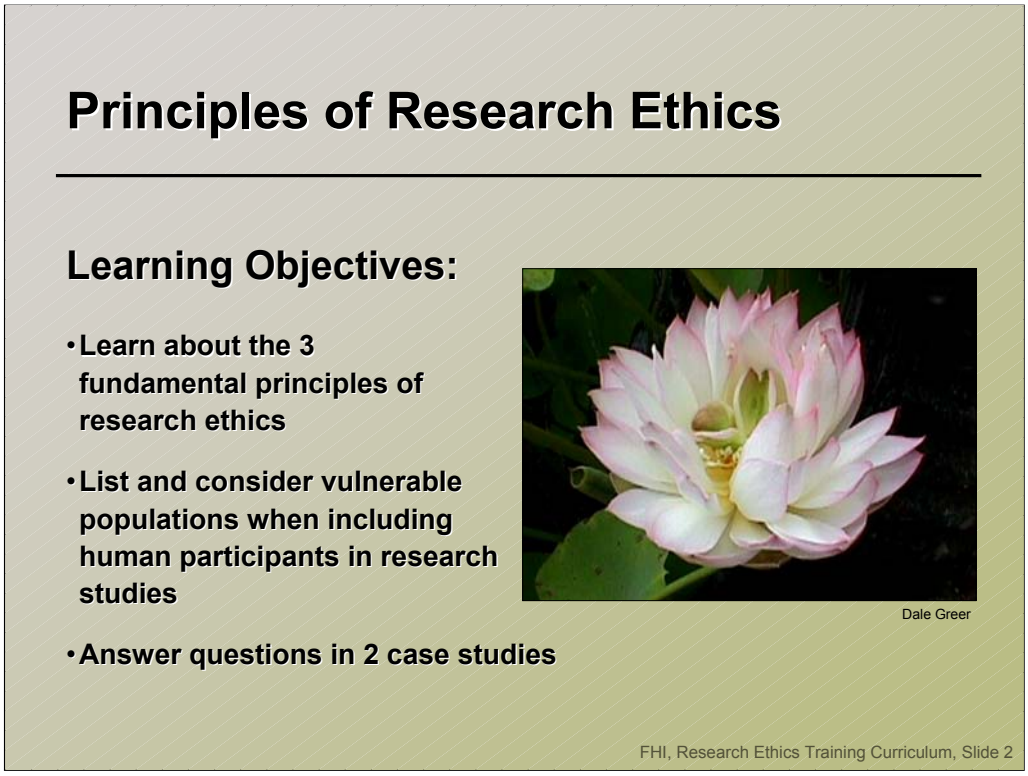
Contents

Slide 1. Overview

This curriculum is made up of 5 chapters, each focusing on a core content area related to research ethics. The core content areas are:

- Principles of Research Ethics
- Foundations of Research Ethics
- Responsible Conduct of Research
- Supervision of Research
- Special Issues in Research

Each chapter of the ***Research Ethics Training Curriculum*** uses the **lotus flower** to symbolize these essential ethical elements. The image represents **purity and perfection** in some cultures. The ethical considerations that are discussed in this curriculum—aiming for a pure and perfect research design—will be the foundation on which the research study is developed and implemented.



Slide 2. Principles of Research Ethics

The learning objectives for the Principles of Research Ethics are:

- Learn about the 3 fundamental principles of research ethics
- List and consider vulnerable populations when including human participants in research studies
- Answer questions in 2 case studies

Slide 3. Fundamental Principles of Human Research Ethics

Human research ethics rest on **3 basic principles** that are considered the foundation of all regulations or guidelines governing research ethics. These principles are:

- **Respect for persons**
- **Beneficence**
- **Justice**

These principles are considered universal, transcending geographic, cultural, economic, legal and political boundaries.

Researchers, institutions, and in fact human society, are obligated to assure that these **principles are followed whenever research on humans is conducted**. Although these principles are universal, the availability of the resources needed to maintain these principles is not universal, and the procedures used for the ethical vigilance of research studies may not be optimal. For instance, no universal principle exists on how a clinical trial should be monitored. Regardless of limitations, these principles must guide the behavior of all individuals involved in planning, conducting and sponsoring human research.

Slide 4. Respect for Persons

Respect for persons recognizes the capacity and rights of all individuals to make their own choices and decisions. It refers to the respect of the autonomy and self-determination of all human beings; acknowledging their dignity and freedom.

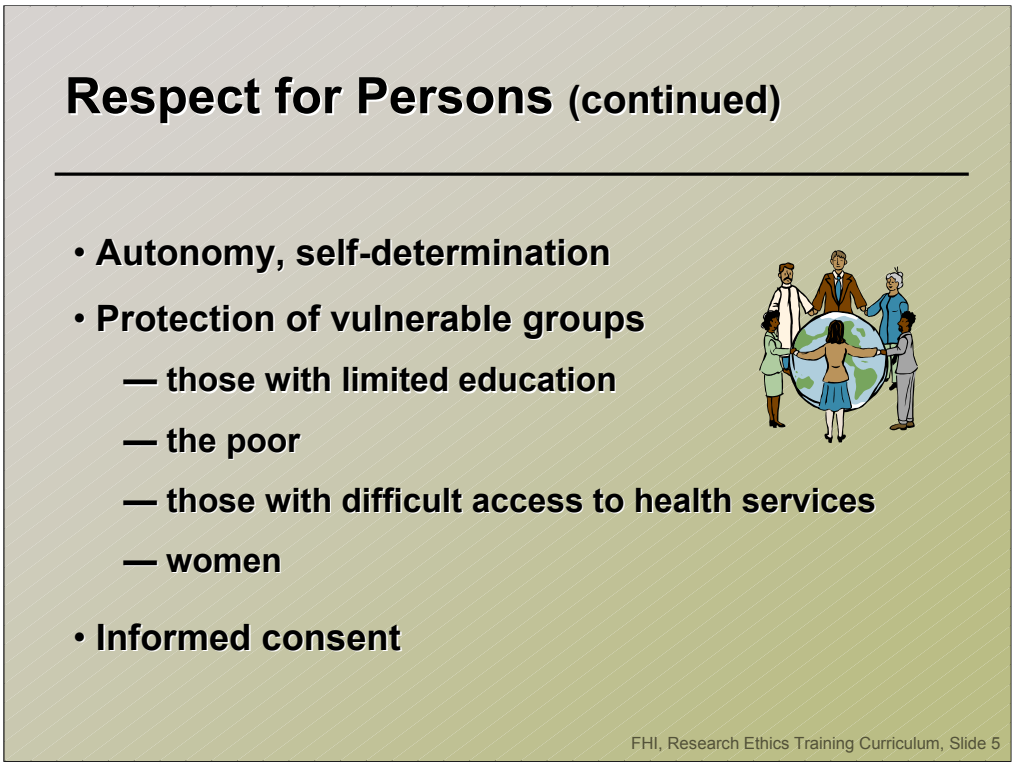
An important component of this principle is the need to provide **special protection to vulnerable persons**.

Learner Note: At this point, list 3 examples of a vulnerable population. Ask participants to call out answers.

1.

2.

3.

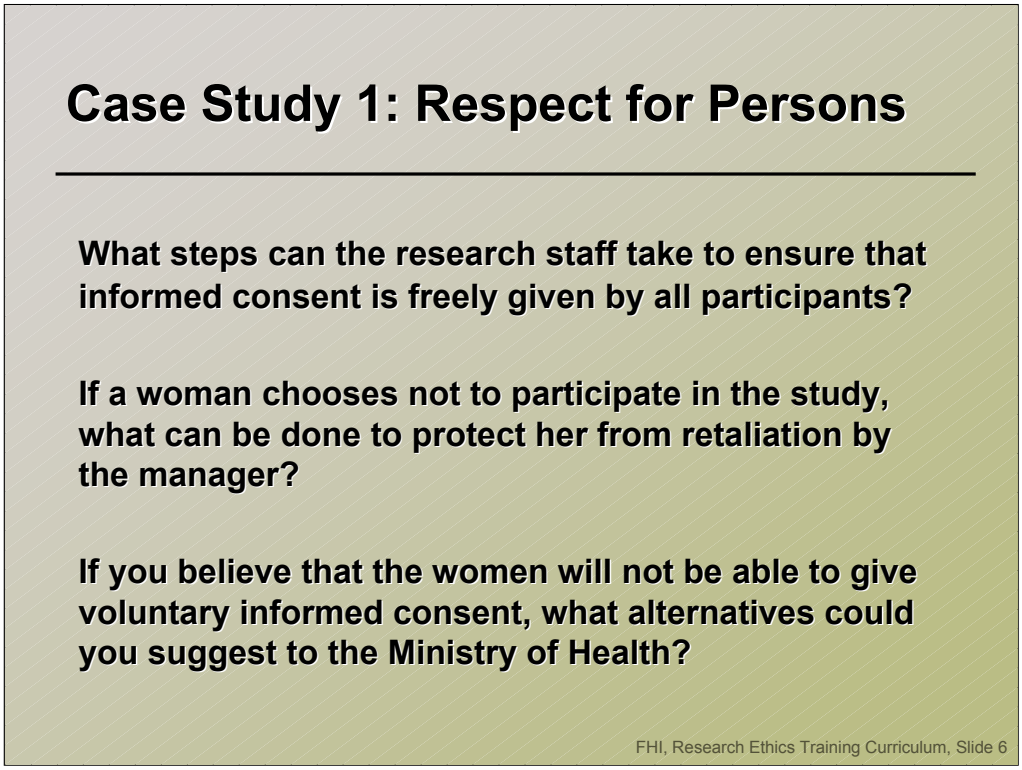


Slide 5. Respect for Persons (continued)

Research among vulnerable groups needs careful attention to protect them. Children, prisoners and the mentally ill are examples of vulnerable groups. People with limited education, living in poverty, or who have limited access to health care services are other examples of vulnerable groups. Women might also be considered a vulnerable group. In some cultures women must defer to men in the decision-making process, making true voluntary consent difficult. These conditions may compromise a person's ability to refuse participation.

Respect for persons is embodied in the informed consent process. Informed consent is designed to empower the individual to make a voluntary informed decision regarding participation in the research. Potential research participants must **fully comprehend** all elements of the informed consent process.

Learner Note: The term "participant" rather than "subject" is used throughout the curriculum. "Participant" is thought to present a more respectful tone, while "subject" may imply a subordinate relationship between the researcher and the volunteer.

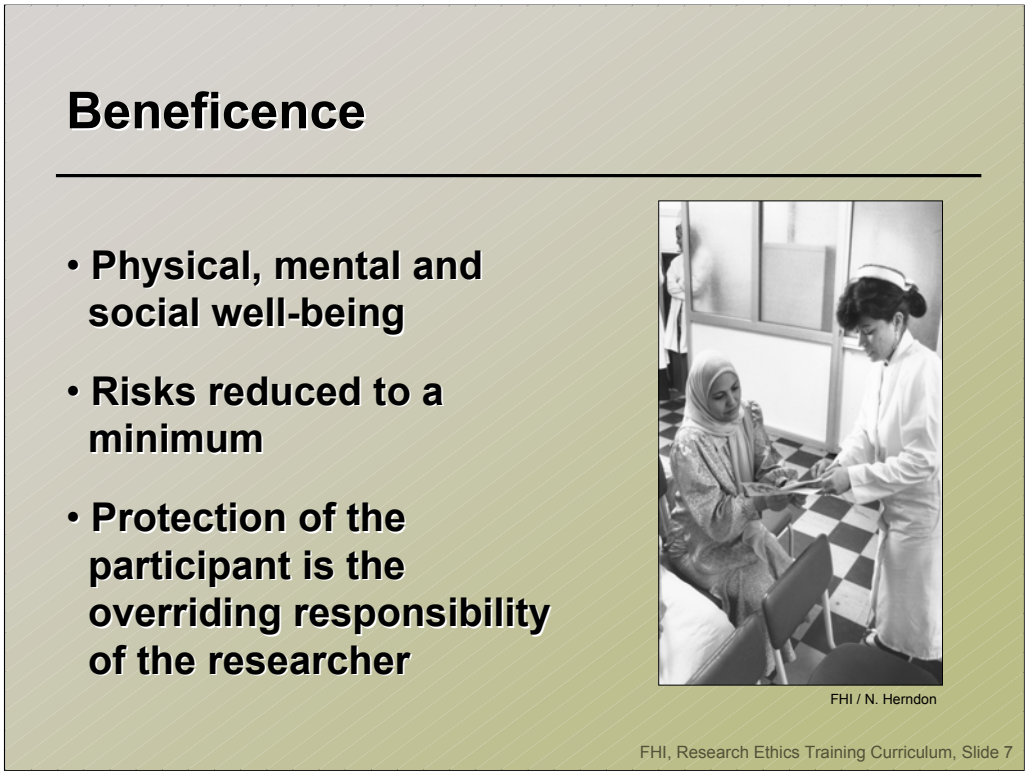


Slide 6. Case Study 1: Respect for Persons

A local Ministry of Health has requested a prevalence/behavioral surveillance study for sexually transmitted infection (STI) among commercial sex workers. Participants in this study will be tested for 3 common STIs and participate in an interview. Participants will receive a card with a number linking them to their blood sample. Women who donate blood will have the option of presenting their card to get the results of the STI tests. Those with positive results for any of the 3 infections will be offered free treatment. In addition, all participants will receive a small gift in return for their participation.

The target population consists of brothel-based sex workers who are strictly controlled by the brothel managers. Prior to initiating the research, the researcher meets with the brothel manager to ask permission to conduct the study. During the meeting, **the manager states that all of the women working in the brothel will participate in the study.**

Learner Note: Make copies of this case study to hand out to small group participants so that they can follow the discussion.



Slide 7. Beneficence

Beneficence makes the researcher responsible for the participant's physical, mental and social well-being as related to the study. Beneficence is also referred to as the principle of *non-maleficence*.

The risks to a person participating in a research study must be weighed against the potential benefit to the participant and the importance of the knowledge to be gained. In any case, all risks should be kept to a minimum.

The protection of the well-being of the participant is the primary responsibility of the researcher. Protecting the participant is more important than:

- the pursuit of new knowledge
- the benefit to science that will result from the research
- personal or professional research interest

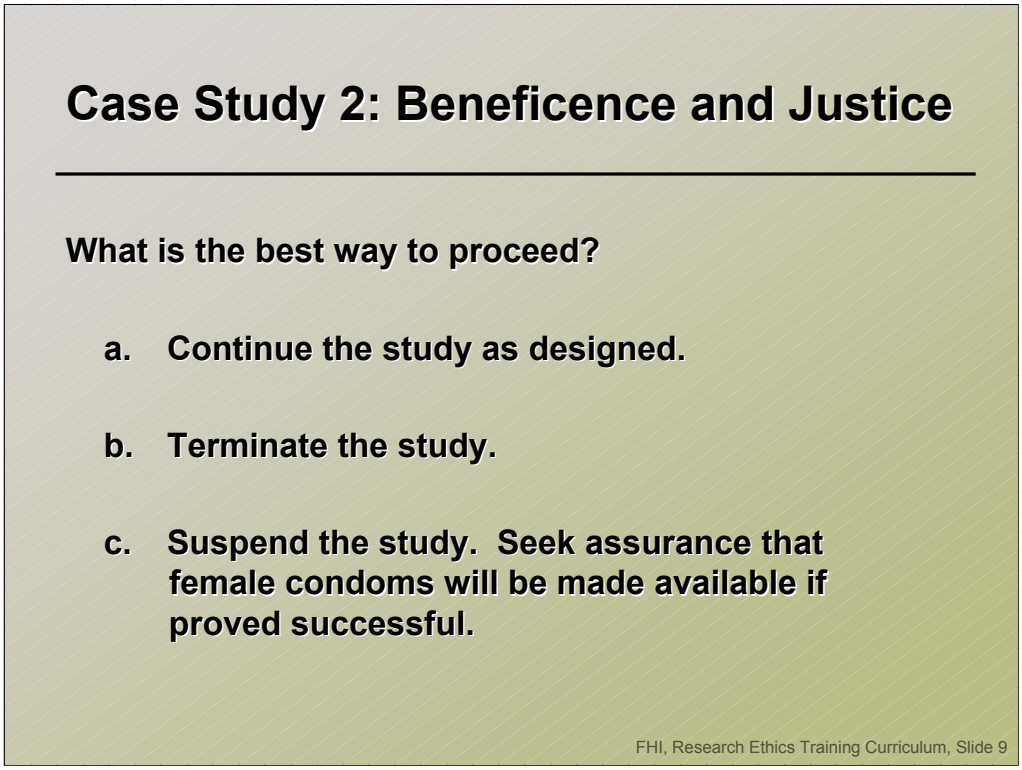
Slide 8. Justice

The researcher's obligation is to **distribute equally the risks and benefits of participation** in the research study**. Recruitment and selection of research participants should be done in an equitable manner.** The principle of justice forbids placing one group of people at risk solely for the benefit of another.

For instance, justice would not permit using vulnerable groups—such as minors, poor people, or prisoners—as research participants for the exclusive benefit of more privileged groups.

As with the principle of respect for persons, there is a need to protect vulnerable groups, including the poor and those with limited access to health services.

Learner Note: When considering the risk/benefit ratio, the ideal is for the benefits to outweigh the risks. However, this can be difficult to attain. For example, Phase I clinical trials do not offer benefit to the participant, who is often a healthy person.



Slide 9. Case Study 2: Beneficence and Justice

A time-series intervention trial was conducted with commercial sex workers. **The goal of the trial was to assess the impact of adding the female condom to a male condom distribution system, measured in terms of a change in the proportion of sex acts protected by condoms.** Condom use was estimated by interviewing study participants about their use of protection in their last 10 sex acts. These measurements were to be made at 5 time points: twice following exposure to male condom promotion and distribution activities, and 3 times following promotion and distribution of both the male and female condom.

The local principal investigator, a highly respected advocate for the sex workers, explained that women were very enthusiastic about participating in the female condom trial, as it would provide them free access to this innovative method of dual protection.

The first round of condom use measurement was completed as planned. Preliminary data analysis revealed that study participants were reporting male condom use in over 95% of sex acts. Following verification of the interviewers' techniques, a second round of interviews was completed. It yielded a similar, exceptionally high-level of male condom use. **There is concern that introducing a new product will have a negative affect on the use of male condoms. In addition, there are questions about the availability and affordability of the female condoms after the conclusion of the study, even if the study is successful.**

Learner Note: Make copies of this case study to hand out to small group participants so that they can follow the discussion.

Slide 10. Foundations of Research Ethics

The learning objective for the Foundations of Research Ethics is:

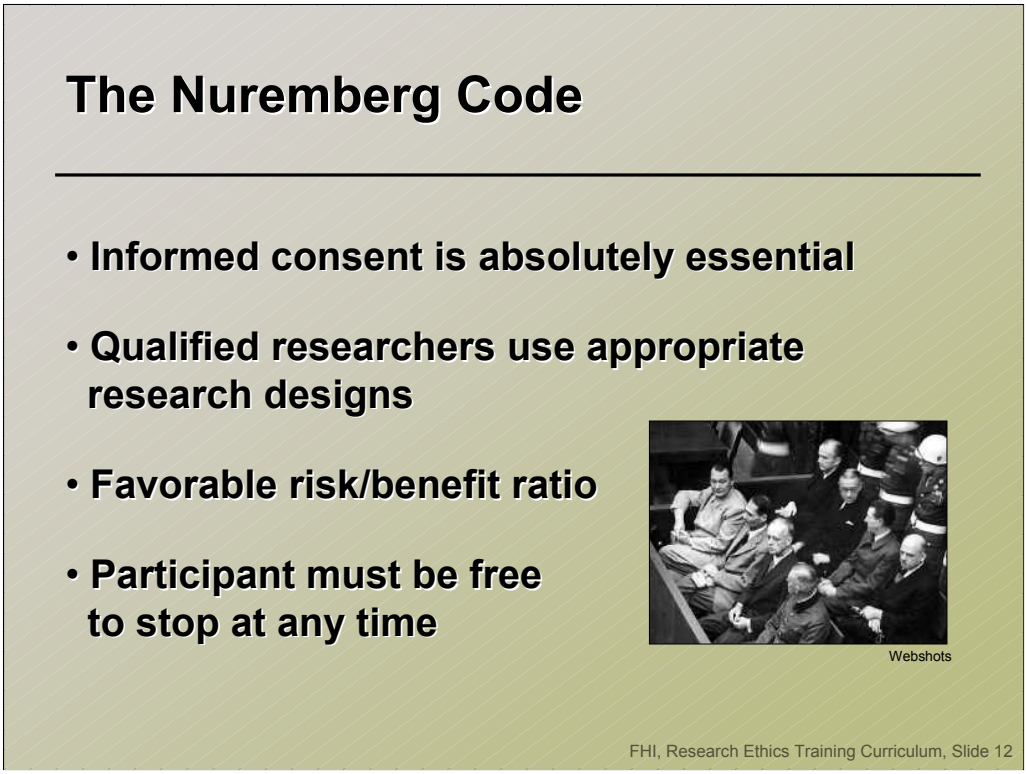
- Discuss some of the incidents and history that have lead to developing universal research ethics

Note that many of the reference documents that are discussed in this chapter are available in the *References* section of this curriculum.

Slide 11. The Evolution of Research Ethics

Guidelines, codes and regulations have been created in recent decades to guide the conduct of research involving human participants. Some of these guidelines were created in response to an ethical lapse. Others were developed to better serve the changing world of research. And still others have evolved since their creation in an attempt to provide answers to new problems and challenges created by the ever-changing research environment. Each reflects the principles of respect for persons, beneficence and justice.

In this chapter of the curriculum, we will look at some of these important codes, guidelines and regulations which should serve as a map for researchers, guiding them towards their scientific end while observing the rules of the road.



Slide 12. The Nuremberg Code

At the end of World War II, the International Military Tribunal prosecuted Nazi war criminals, including Nazi doctors who performed experiments on concentration-camp prisoners. The tribunal's decision includes what is now called the *Nuremberg Code*, a 10-point statement outlining permissible medical experimentation on human participants.

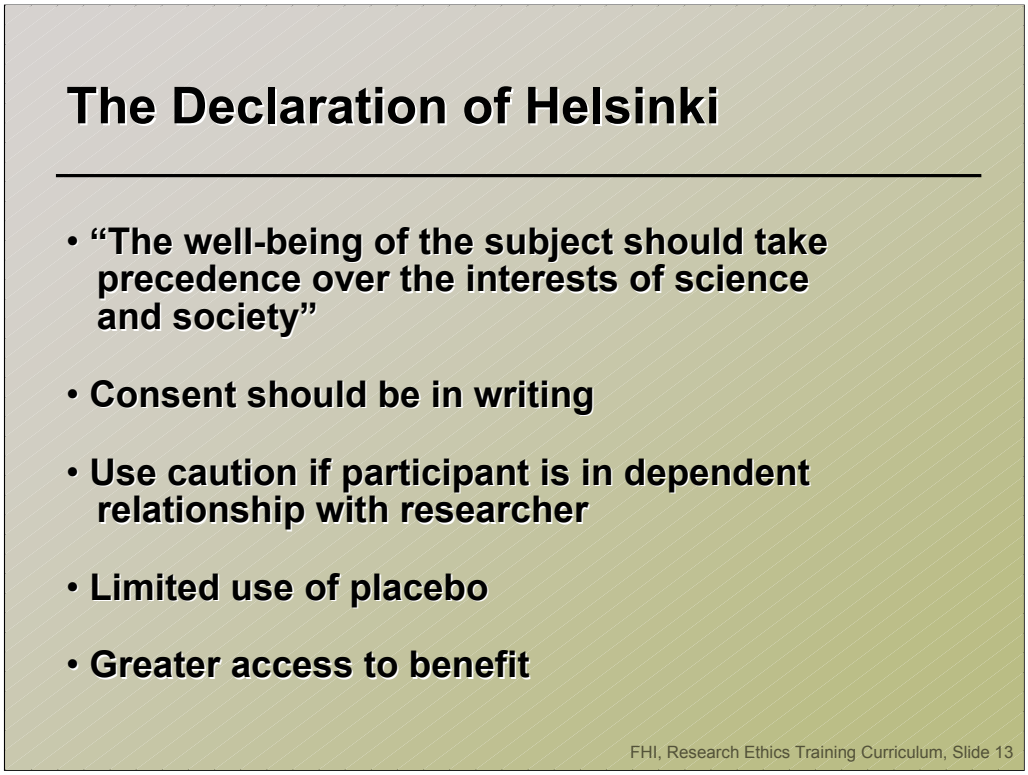
The code clarified many of the basic principles governing the ethical conduct of research. The first provision of the code requires that "**the voluntary informed consent of the human subject is absolutely essential**." The code provides other details implied by such a requirement:

- capacity to consent
- freedom from coercion
- comprehension of the risks and benefits involved

Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified researchers using appropriate research designs, and freedom for the participant to withdraw at any time.

The code does not specifically address clinical research in patients with illnesses, an oversight addressed in later codes and regulations.

Learner Note: The full text of the *Nuremberg Code* may be accessed on the Internet at *http://ohsr.od.nih.gov/nuremberg.php3*.



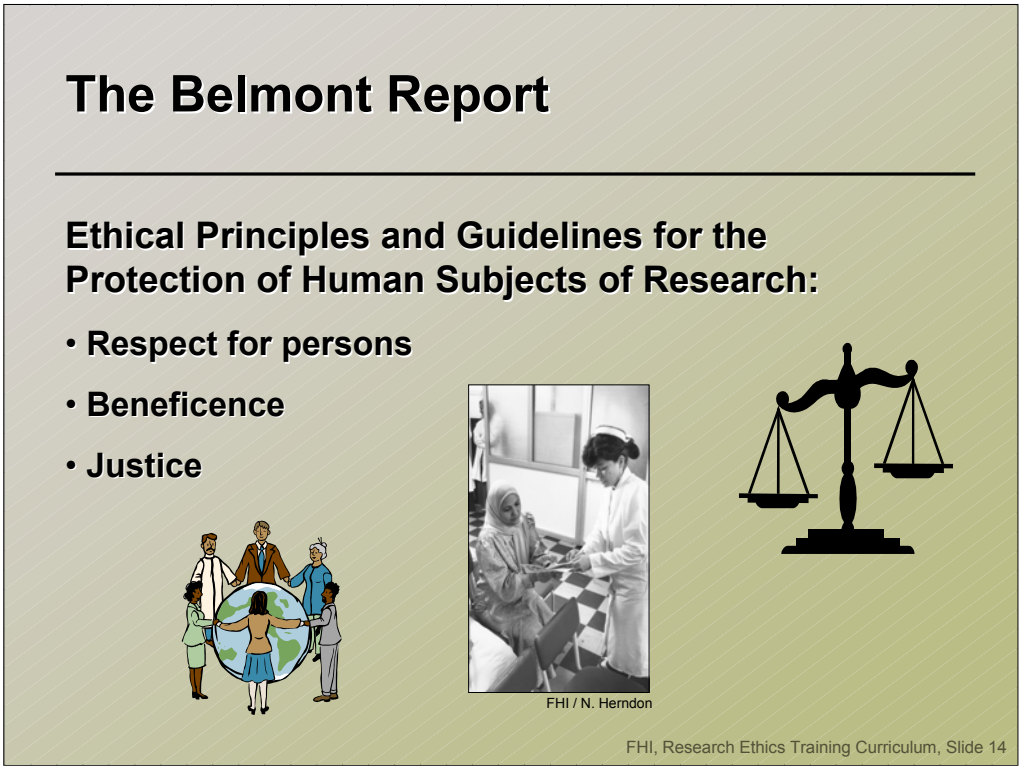
Slide 13. The Declaration of Helsinki

Recognizing the shortcomings of the *Nuremberg Code*, the World Medical Association created the *Declaration of Helsinki* in 1964. Considered by many to be the first world standard for biomedical research, this document provides for extra protection for persons with diminished autonomy and urges caution on the part of the physician-researcher who enrolls his own patients.

At the heart of the declaration is the principle that the well-being of the participant should take precedence over the interests of science and society. It also **recommends written consent forms.** Like the *Nuremberg Code*, it requires that risks be reduced to a minimum.

Since its creation, the *Declaration of Helsinki* has been revised 5 times. It was most recently revised in 2000, following the heavy criticism of placebo-controlled AZT studies in Africa. In this revision, the use of placebo controls has been limited to special circumstances and is not recommended in cases where a proven prophylactic, diagnostic or therapeutic method exists. The current version also requires access to benefits for all study participants.

Learner Note: The full text of the *Declaration of Helsinki* is included in the *References* section of the curriculum.



Slide 14. The Belmont Report

In 1972, the public became aware of the Tuskegee study, which took place in the southern United States from 1932 to 1972. More than 400 men with latent syphilis were followed for the natural course of the disease rather than receiving treatment. The study continued to deny men treatment even after antibiotics were discovered in the 1940s. This study was all the more infamous because the participants were all poor African-Americans, a disadvantaged group in the southern United States at the time.

As a result, in 1974 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established. In 1978, the commission submitted its report titled, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. The report sets forth the fundamental ethical principles underlying the acceptable conduct of research involving human participants.

Those principles—respect for persons, beneficence and justice—are accepted as the 3 fundamental principles for the ethical conduct of research involving human participants.

Learner Note: The full text of *The Belmont Report* is included in the *References* section of the curriculum.

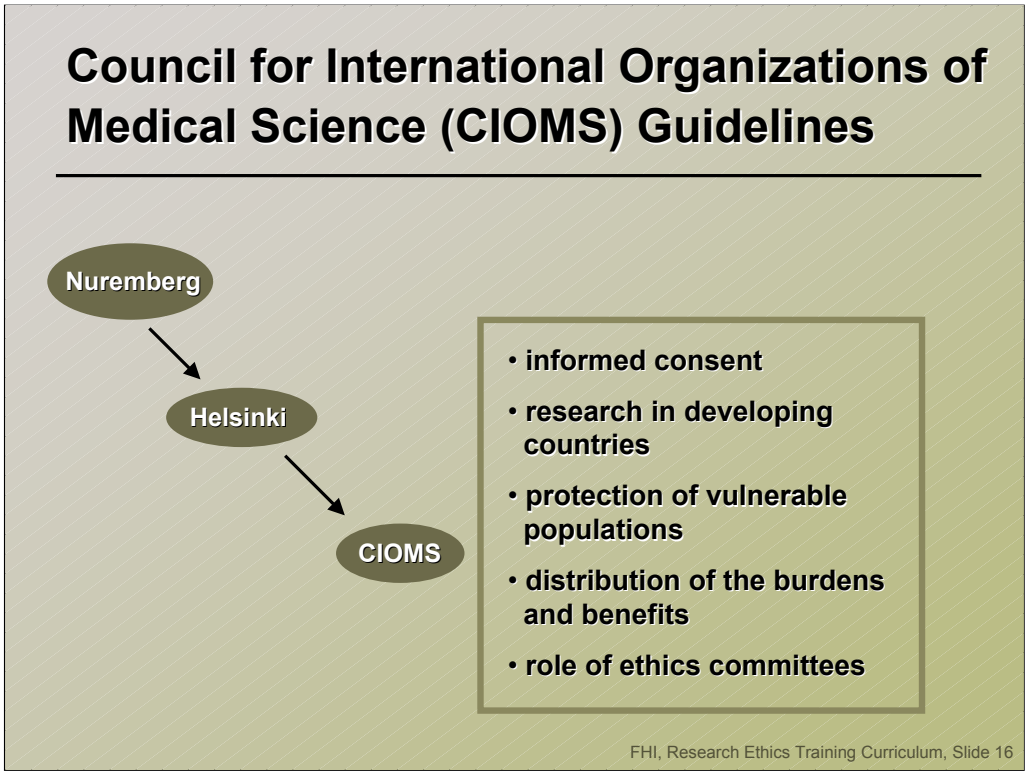
Slide 15. The U.S. Code of Federal Regulations (also called *The Common Rule*)

This code applies to all research sponsored by the U.S. government. In 1991, *The Federal Policy* (referred to as *The Common Rule*) was adopted by 16 federal agencies that conduct, support or otherwise regulate human participant research in the United States. As is implied by its title, *The Common Rule* is designed to standardize the human participant protection system in all relevant U.S. federal agencies and departments.

***The Common Rule* requires:**

- **prior ethics committee approval**
- **written informed consent and documentation**
- **equitable recruitment of research participants**
- **special protection for vulnerable groups**
- **continuing review of approved research**

Learner Note: The full text of *The Common Rule* is included in the *References* section of the curriculum where it appears as *45 CFR 46*.



Slide 16. Council for International Organizations of Medical Science (CIOMS) Guidelines

CIOMS has been active in bioethics for many years. In 1993, CIOMS issued the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, with the purpose to indicate how the ethical principles of the *Declaration of Helsinki* can be applied effectively, particularly in developing countries.

The **guidelines are based on the 3 principles of research ethics** and consist of 15 guidelines, each followed by interpretive commentary. The topics include:

- **informed consent**
- **research in developing countries**
- **protection of vulnerable populations**
- **distribution of the burdens and benefits**
- **role of ethics committees**

Also included are the obligations of the sponsor, the researcher, and the host country. Due to their global applicability, the guidelines have been widely disseminated and adopted.

Learner Note: The full text of the *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects* is included in the *References* section of the curriculum.

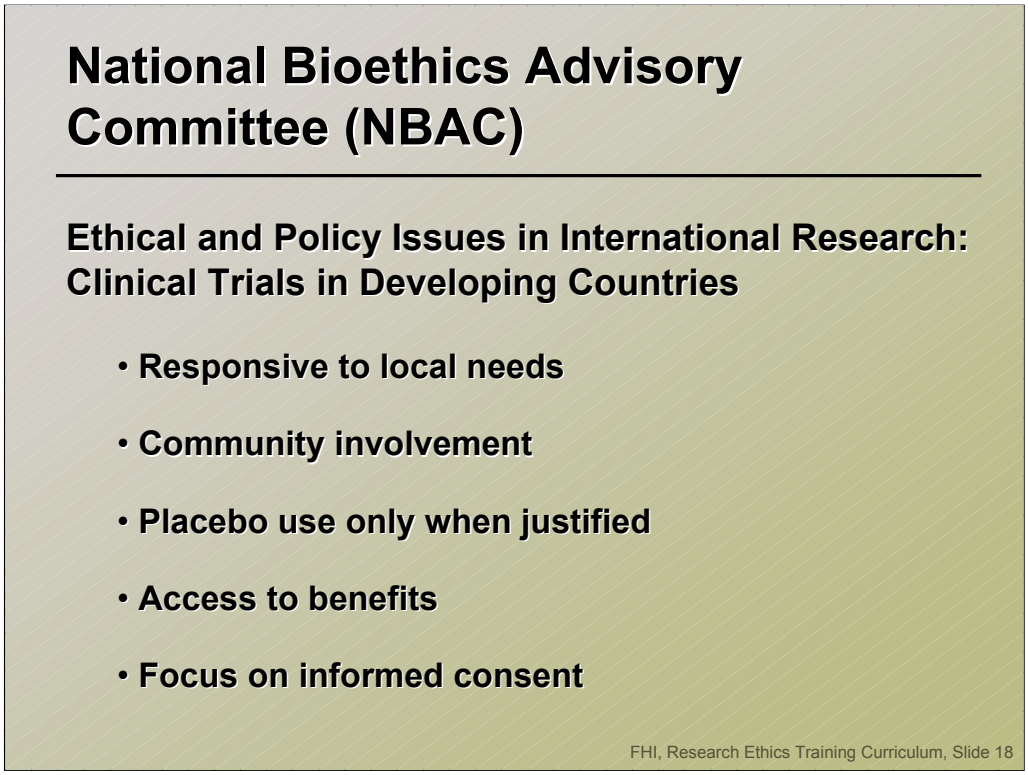
Slide 17. International Conference on Harmonisation (ICH)

In the 1960s and 1970s, many countries enacted laws and **regulations for reporting and evaluating the data on safety, quality and efficacy of new medical products**. Although different regulatory systems were based on the same fundamental obligations, the requirements were not uniform.

In 1990, representatives of the regulatory agencies and industry associations of the United States, Japan and Europe met and formed the International Conference on Harmonisation (ICH), with the goal **to standardize the process by which new drugs are developed, tested and brought to market.** In 1996 the ICH finalized the *Guideline for Good Clinical Practice (GCP)*. The introduction to the guideline states that GCP is "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human subjects." Many pharmaceutical companies have adopted the *GCP* as the standard for conducting clinical trials.

The ICH guidelines require **review by an ethics committee** and **informed consent of participants**. In addition, the guideline details the responsibilities of both the **sponsor** of the research and the **researcher** who conducts it.

Learner Note: The full text of *ICH Guideline* may be accessed on the Internet at *http://www.ich.org.*

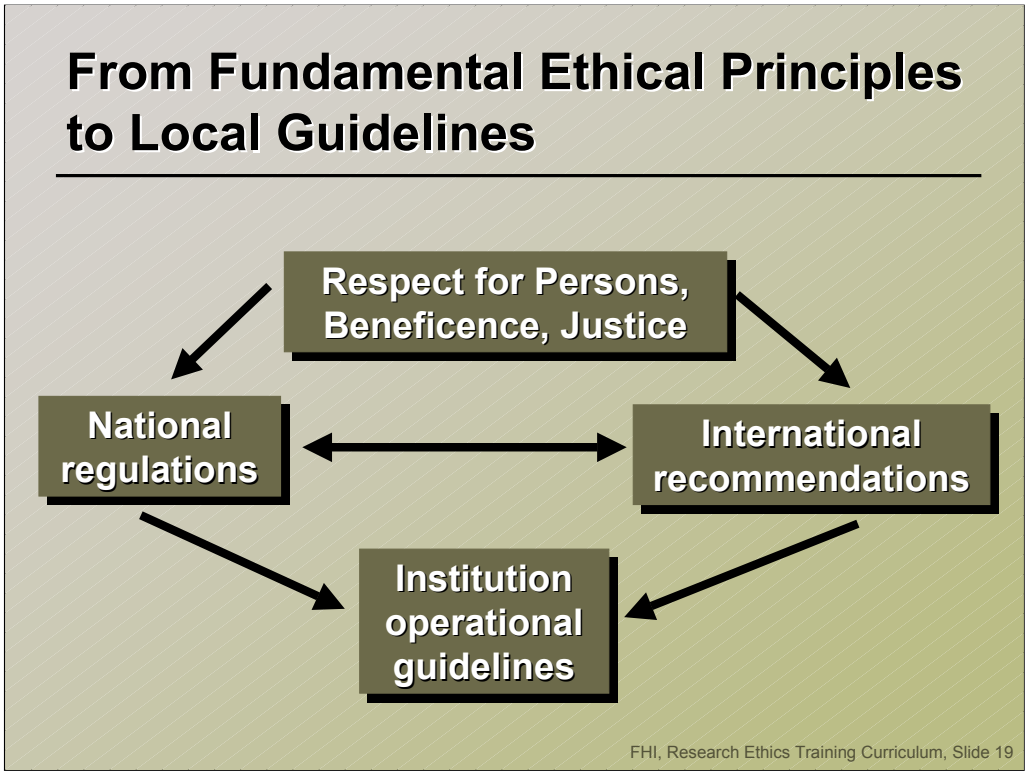


Slide 18. National Bioethics Advisory Committee (NBAC)

NBAC advises the President of the United States on matters related to research involving human participants. In 2001, the NBAC published a report that **requires that all research in developing countries address a local health need**. Additionally, the researchers and sponsors should **involve representatives of the community and potential participants** throughout the design and implementation of the research.

In the design of studies, researchers must justify the use of placebo and, when possible, provide members of the control group with an established, effective treatment, **regardless of local availability**. Researchers and sponsors should make efforts to **ensure access to benefits** for study participants and the larger host community.

Another major focus of the report is the informed consent process. The NBAC states that the **informed consent process must be culturally appropriate**. Also, the process should minimize all coercion or undue inducement on the part of the researcher and community representatives. **All participants must be free to make a voluntary decision regardless of sex, socioeconomic status, or their role in a culture**.



Slide 19. From Fundamental Ethical Principles to Local Guidelines

The 3 fundamental principles of human research ethics—respect for persons, beneficence and justice—are the foundations for research ethics. These principles are commonly embodied in national regulations or international recommendations.

Eventually, these regulations and recommendations need to be adapted or transformed into institution operational guidelines to be **used at the local level to guide the planning, review, approval and conduct of human research.**

In this process, fundamental principles are applied within the context of local laws and cultural and economic circumstances.

Slide 20. Local Regulations and Guidelines

Throughout the world, countries where research is taking place are at various stages in the development of national human research ethics regulations and the establishment of an infrastructure to supervise such research. **The rapid rise in the amount of research on human participants conducted in these countries has further exposed the need for local regulations and support mechanisms.**

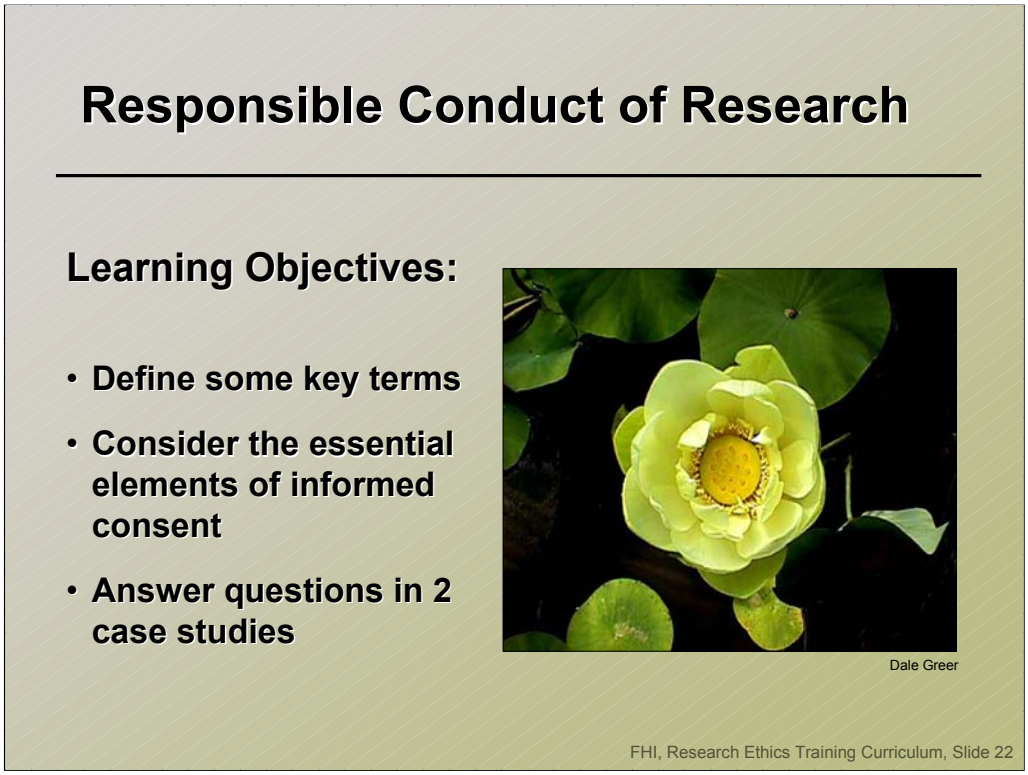
Some countries have very advanced national guidelines to conduct human research. For example, guidelines now exist in Brazil, India, South Africa, Thailand, and Uganda. However, many other countries lack established guidelines or are at the beginning of the development process. **In much of the developing world, there remains an urgent need for regulations**. While existing international recommendations, such as the *Declaration of Helsinki* or the *CIOMS International Ethical Guidelines*, are important references, they are not a substitute for national or local regulations.

Learner Note: Does your country have established guidelines for the conduct of research? Does your local institution?

Slide 21. Summary—Principles and Foundations of Research Ethics

Research with human participants is a privilege, not a right. Researchers and scientists work within the framework of society, and the rules of society must be followed vis-à-vis the rules of science and research. While there are currently many different guidelines governing research with human participants, all share the same fundamental principles of research ethics. **Each demands from the researcher respect for persons, beneficence and justice.**

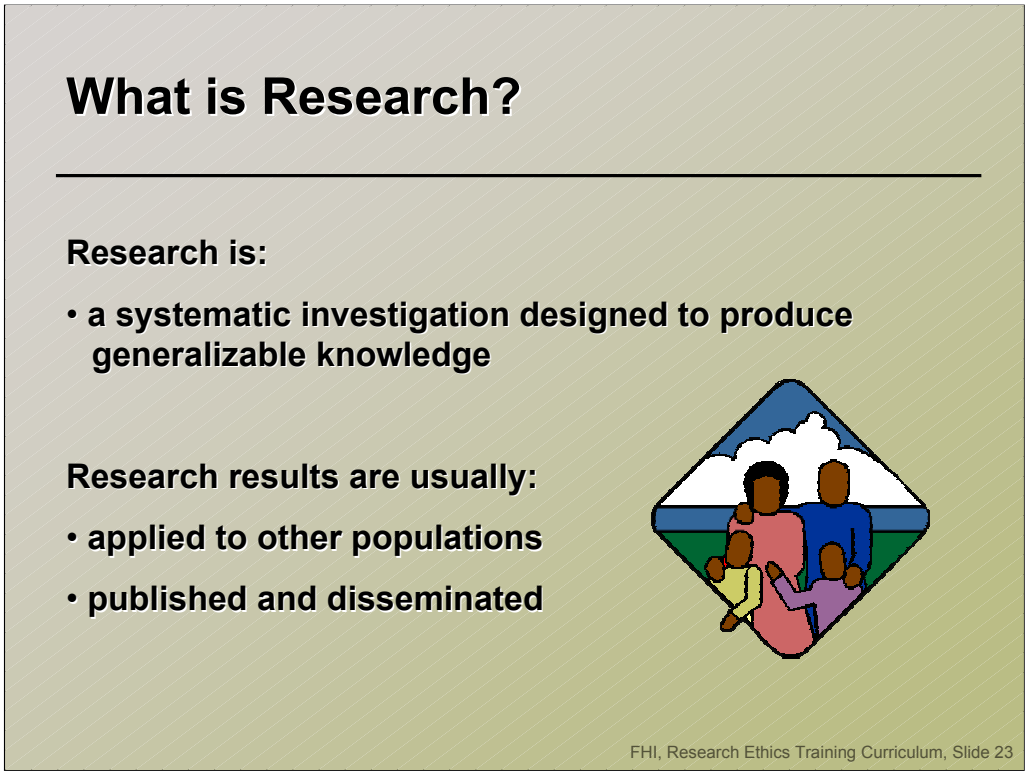
However, merely meeting the letter of the law is insufficient. The research community must strive to meet, if not exceed, the spirit contained in the guidelines. In doing so, they place the well-being of the individual research participant before everything else.



Slide 22. Responsible Conduct of Research

The learning objectives for the Responsible Conduct of Research are:

- Define some key terms
- Consider the essential elements of informed consent
- Answer questions in 2 case studies



Slide 23. What is Research?

Ethical considerations are particularly important in research studies that require the participation of human participants. Therefore, it is essential to define **what is research** and **who are research participants**.

The Common Rule defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." The words *systematic* and *generalizable* are key words in the definition.

Systematic: **An organized, formally structured methodology to obtain new knowledge**. It commonly implies the development of a research protocol with clearly stated objectives.

Generalizable: **The obtained knowledge is intended to have a broad or general application beyond the group that participated in the research**. The new knowledge will have applications beyond the study setting.

Commonly, the results of the research will be published and widely disseminated and used.

Slide 24. Who are Research Participants?

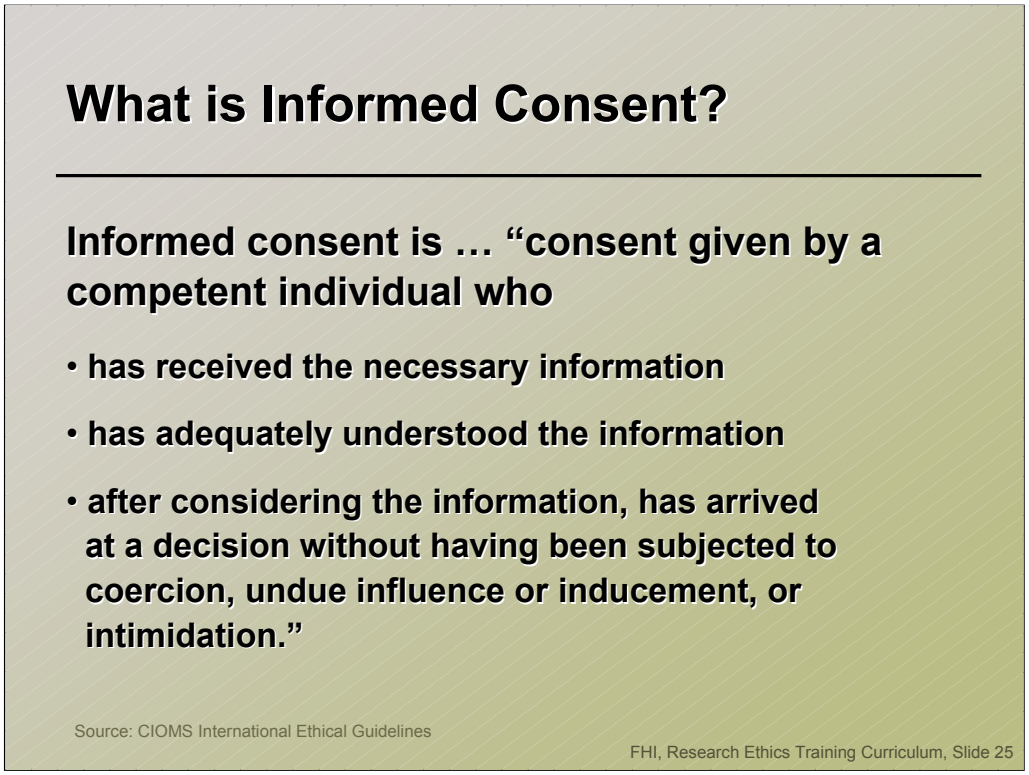
The Common Rule defines research participants as living individuals about whom a researcher (whether professional or student) conducting research obtains:

- data through intervention or interaction with the individual
- identifiable private information

Intervention: includes **not only physical procedures, but also the manipulation of the participant's environment** for the purpose of the research.

Interaction: includes **communication or interpersonal contact between researcher and participant**.

Private information: includes **information provided by the participant that can be reasonably expected to be kept confidential**. Private information must be individually identifiable to constitute research.



Slide 25. What is Informed Consent?

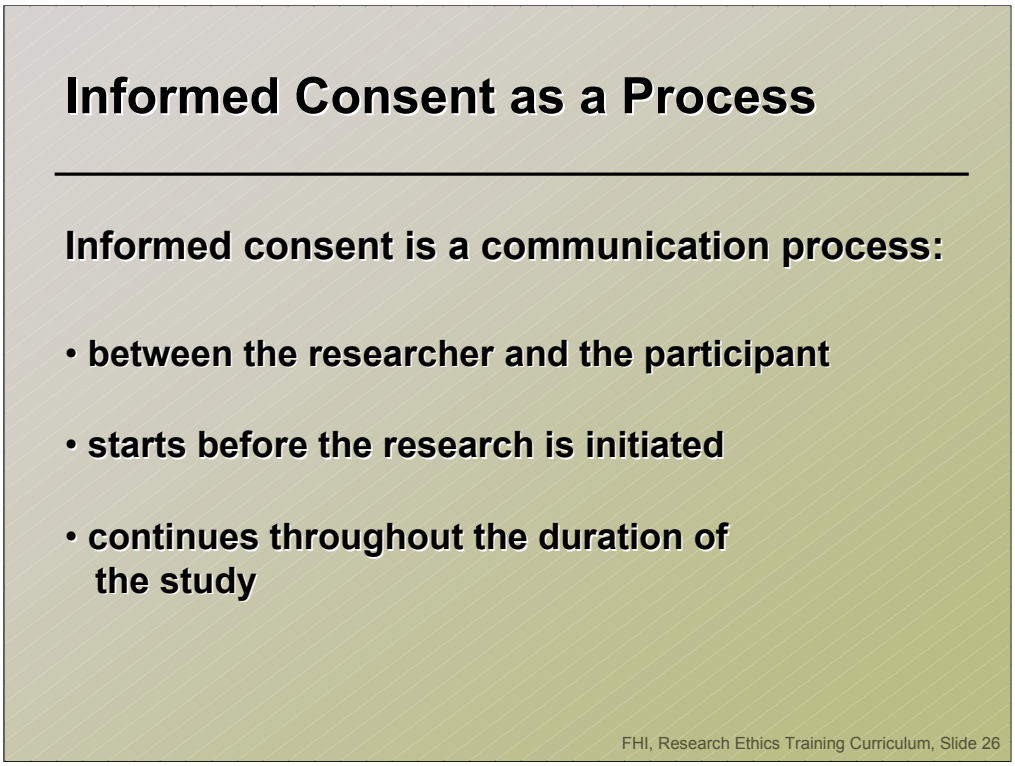
It is **essential to obtain informed consent from participants in a human research study before the study is initiated**.

The *CIOMS International Ethical Guidelines* define informed consent as "consent given by a competent individual who

- has received the necessary information
- has adequately understood the information
- after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation."

Learner Note: Ask the audience to identify examples of individuals whom the CIOMS guidelines may not consider to be competent. (Some examples: young children, the mentally ill, people with severe mental disorders, people unfamiliar with modern medical concepts.)

Give examples of necessary information items that may be included in the informed consent process.



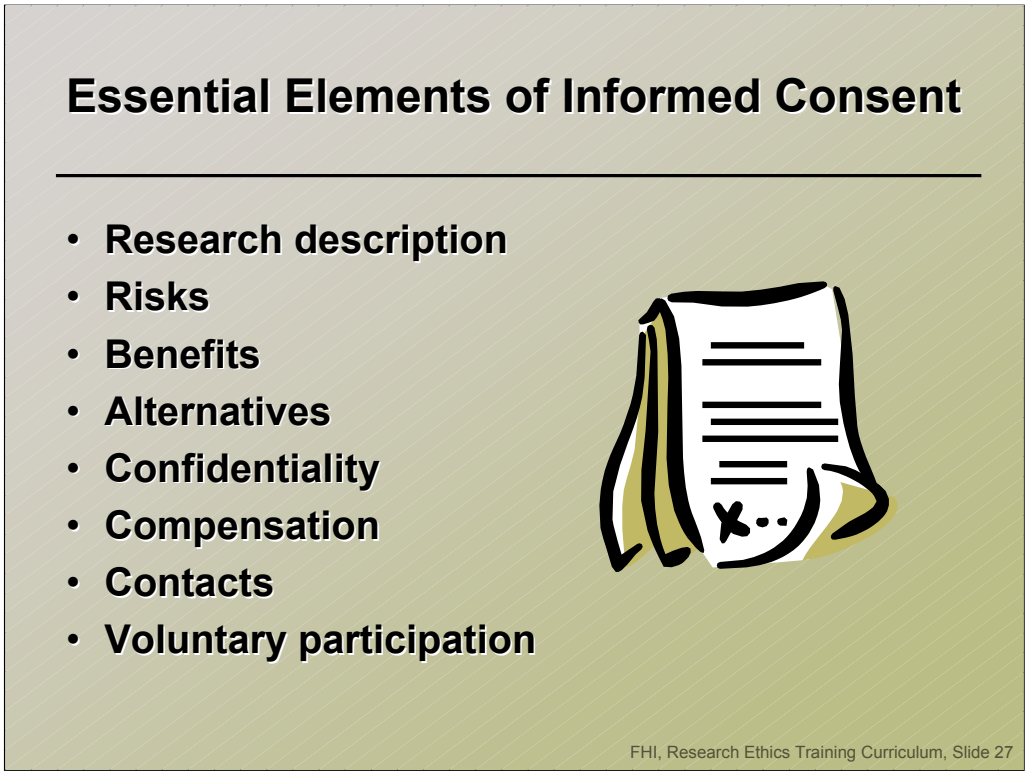
Slide 26. Informed Consent as a Process

Informed consent embodies the fundamental ethical principle of respect for persons, of their autonomy, rights and capacity to make informed choices.

Informed consent is not merely a legal requirement or a document to be signed; **it is a communication process between the researcher and the participant** that starts before the research is initiated and continues throughout the study. It is essential that the information provided is understood by the potential participant and empowers that person to make a voluntary decision about whether or not to participate in the study.

The type, extent and method of the information provided requires the review and approval of an appropriate ethics committee.

Learner Note: The role of the ethics committee is described later in this curriculum.



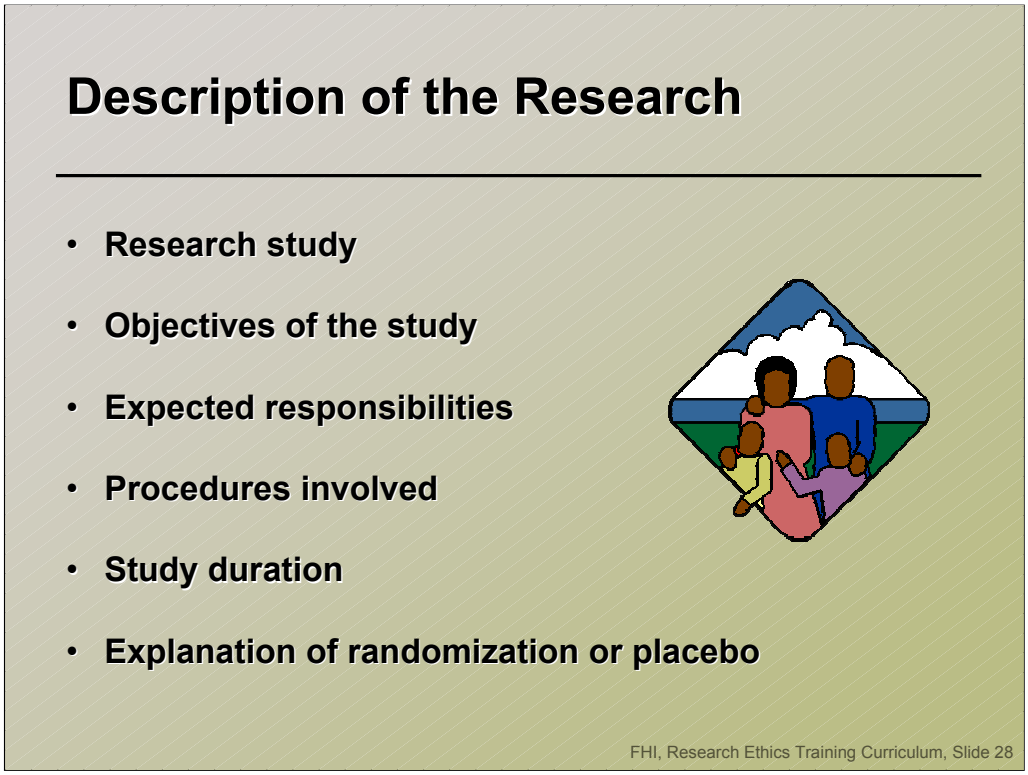
Slide 27. Essential Elements of Informed Consent

According to *The Common Rule*, in order to ensure that a research participant receives the necessary information to make an informed decision, it is important to provide each participant with:

- **description of the research and participant's participation**, including identification of experimental procedures
- description of reasonably **foreseeable risks**
- description of **expected benefits**
- potentially **advantageous alternatives** to participation
- explanation of **confidentiality**
- explanation of **compensation for injuries**
- **whom to contact** about the research and participants' rights
- explanation that participation is **voluntary**

The informed consent process is basic to a well-designed, ethically based research study. How informed consent is applied to the research study demands time, creativity, and an understanding of the participant population.

Learner Note: List some of the problems that may be encountered getting informed consent with your research participants.

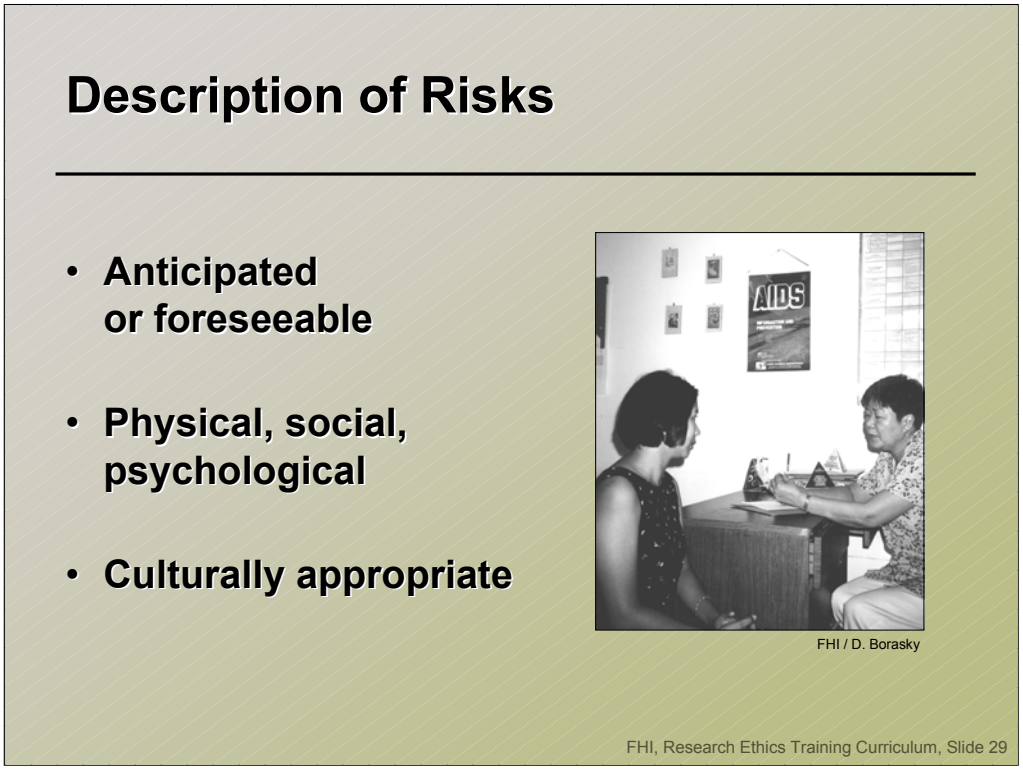


Slide 28. Description of the Research

Typically, the initial information provided in the informed consent is **a clear, direct statement that the study involves research** and is therefore seeking answers to unknown questions. The purpose or objectives of the research must be clearly presented, explaining what new information the study is seeking to obtain. In clinical research, potential participant must understand that they will not be receiving standard or regular health care services.

Participants must agree to be subjected to the procedures required by the study, particularly to those procedures that are **experimental**. The anticipated duration and the expected participant responsibilities of the study must be clearly stated and agreed upon by participants.

If the study involves randomization and the possible use of a placebo, then participants should understand that they may not be receiving any actual treatment.



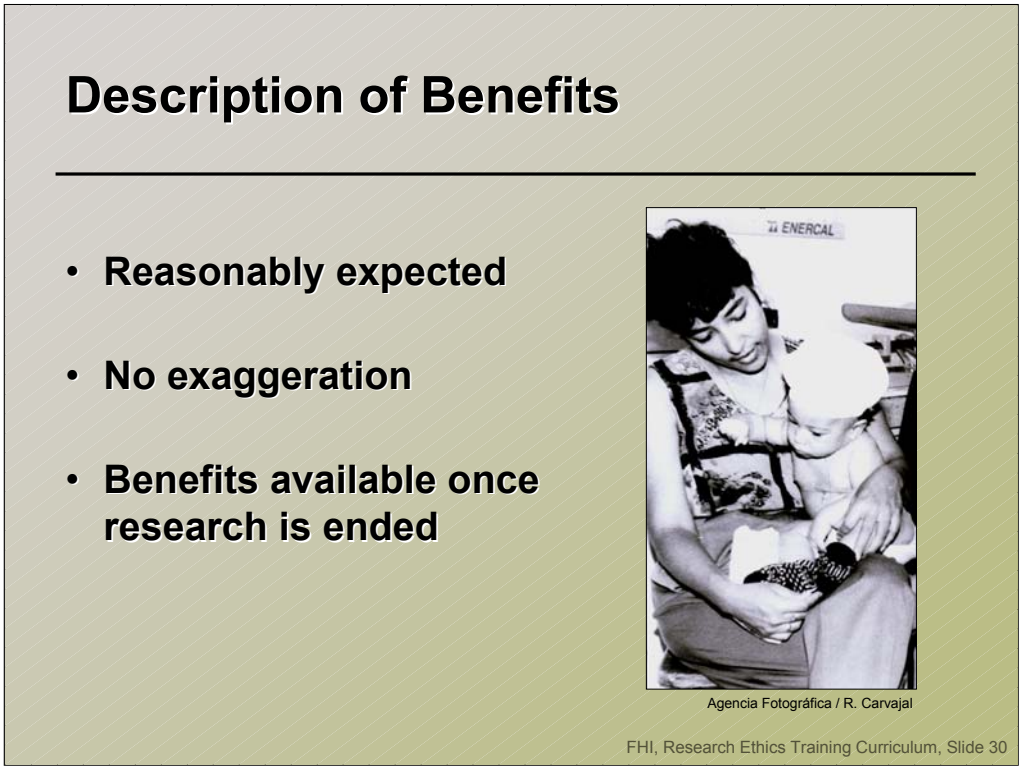
Slide 29. Description of Risks

In the informed consent process, the anticipated or reasonably foreseeable risks, **including physical, social and psychological,** associated with participation in the study must be carefully explained.

The amount of information on possible risks, and how it is presented, requires special consideration in the planning of the informed consent process. Cultural influences and established local medical practices should be considered.

The way risks will be presented to the participant requires the review and approval of an ethics committee. If any new risks are identified during the research, the informed consent must be revised and all the participating individuals must be promptly notified.

Learner Note: Give examples of problems associated with description of risks in your informed consent process.



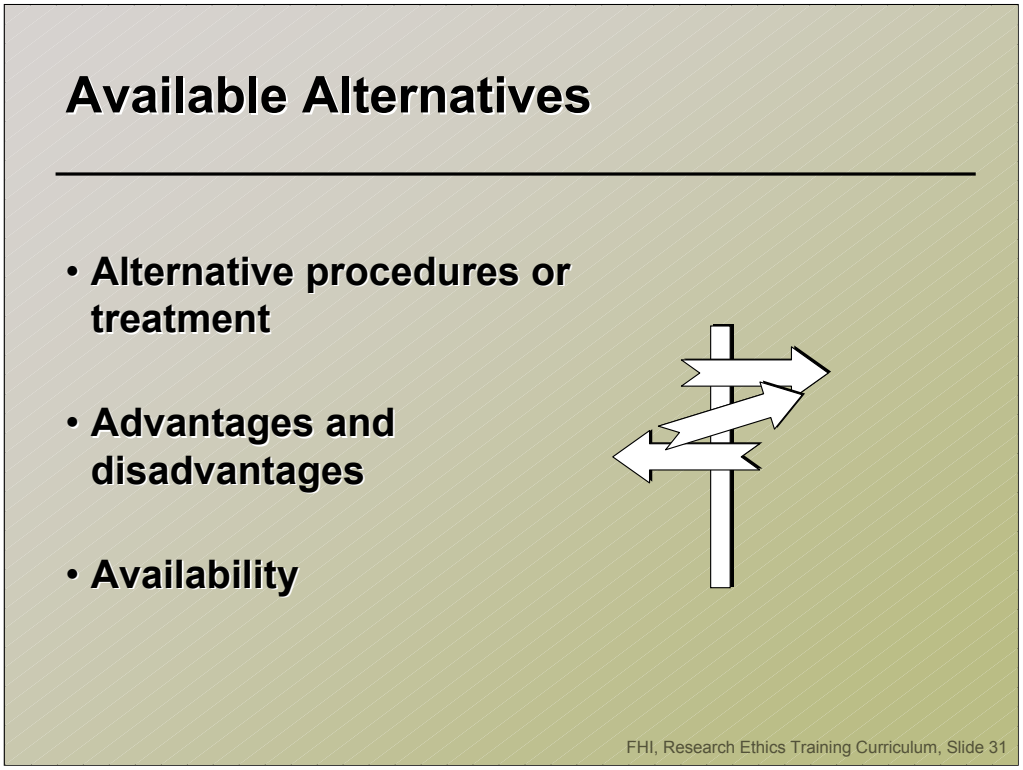
Slide 30. Description of Benefits

Research participants must be advised about possible benefits resulting from participation in the research. According to *The Common Rule*, "the informed consent must include a description of any benefits to the subject or to others which may reasonably be expected from the research."

The benefits must not be exaggerated and never used to mislead the participant into participating in the research study. The free provision of health services, to which the participant is otherwise entitled, must not be presented as a special benefit.

Special care is needed in the way benefits are presented to individuals with limited access to health care services. Offering health care to individuals who would otherwise not have access is a powerful incentive that is potentially coercive. Researchers are responsible for ensuring that potential participants' decisions are not clouded by the promise of health care.

Finally, information about what benefits or services will be available to participants when the research has ended needs to be described in the informed consent form.

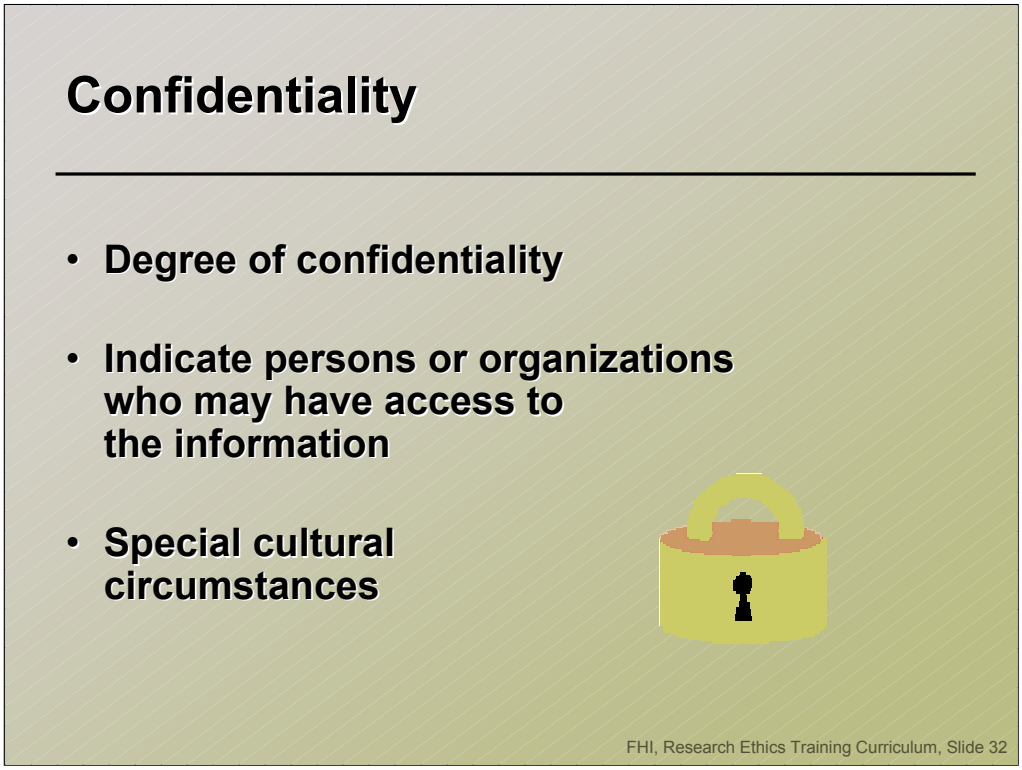


Slide 31. Available Alternatives

In the informed consent form, *The Common Rule* indicates that "subjects must be made aware of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject."

In order to do this, **the informed consent form must describe treatment alternatives that exist—including other options to participating in the research.**

Descriptions of alternatives should enable the participant to choose between research procedures or standard procedures.



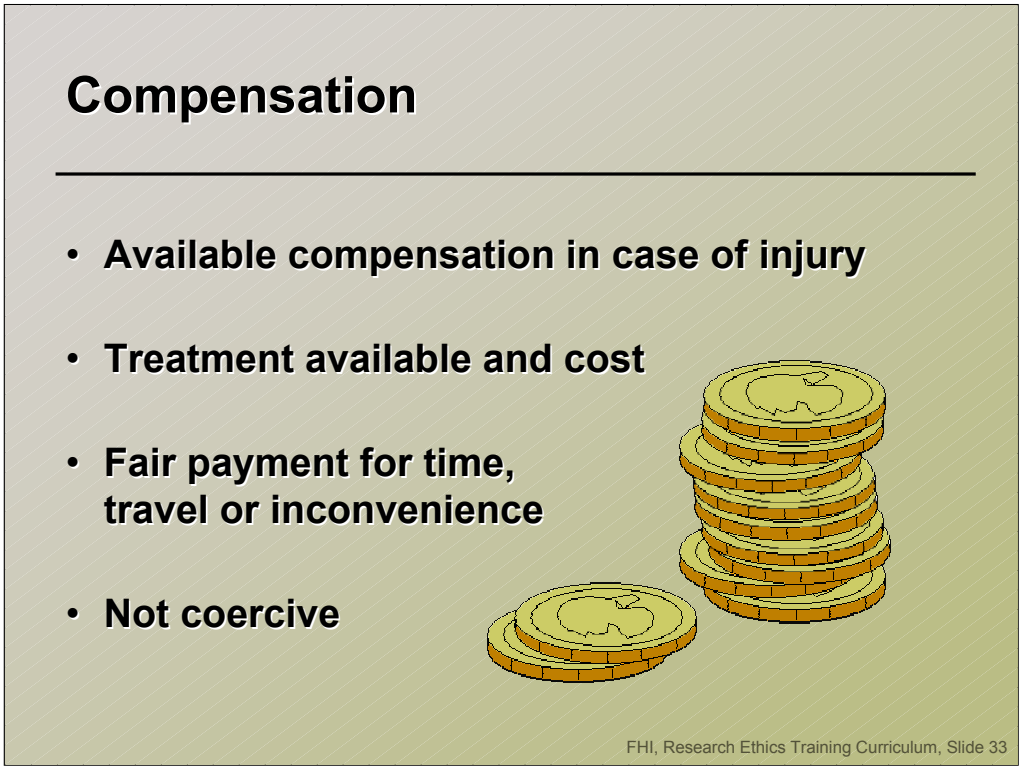
Slide 32. Confidentiality

In the informed consent form, the **degree of confidentiality that will be provided should be given.** This information should include the names of people or organizations that may review the research records.

If the researcher's ability to protect any confidential information is limited, the extent of this limitation must be disclosed to the potential participant.

Special attention to confidentiality is necessary when public **knowledge of participation is potentially damaging**. Sometimes the greatest risk to the participant is a breach of confidentiality.

Learner Note: List breaches of confidentiality that you have heard about in research. How would you handle these situations? Give examples of situations where a breach of confidentiality may be damaging to a participant. For example, a woman may be abused by her partner as a result of participating in research. Give examples of persons or organizations that often review research records.



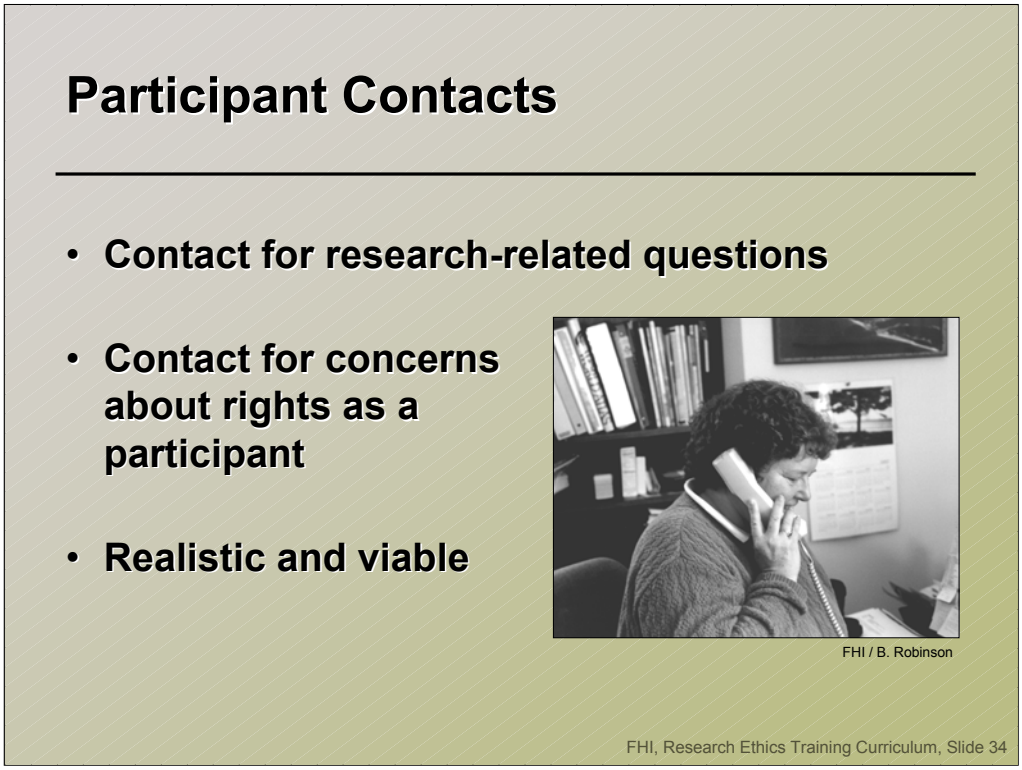
Slide 33. Compensation

According to *The Common Rule*, **clear information must be provided about any compensation** that may be available to the participant if a problem arises during the study. Information must be disclosed about the treatment that would be available and who would pay for it in the case of injury or complications.

The CIOMS guidelines recommend that "compensation is owed to subjects who sustain significant physical injury from procedures performed solely to accomplish the purpose of research." However, not all organizations do so. Researchers must be aware of institutional and sponsor policies on the compensation of participants.

It is permissible **to compensate participants for their time, travel and inconvenience**. The amount of this compensation should be reasonable and based on local costs.

Compensation should not be so high as to unduly influence a potential participant's decision to participate in the study. This is especially important when the participant population is impoverished.



Slide 34. Participant Contacts

In the informed consent form, **information must be provided on whom to contact if a research-related question arises**. Thought must be given to how contact can best be made by the research participants. As much as possible, contact persons should be available at all times.

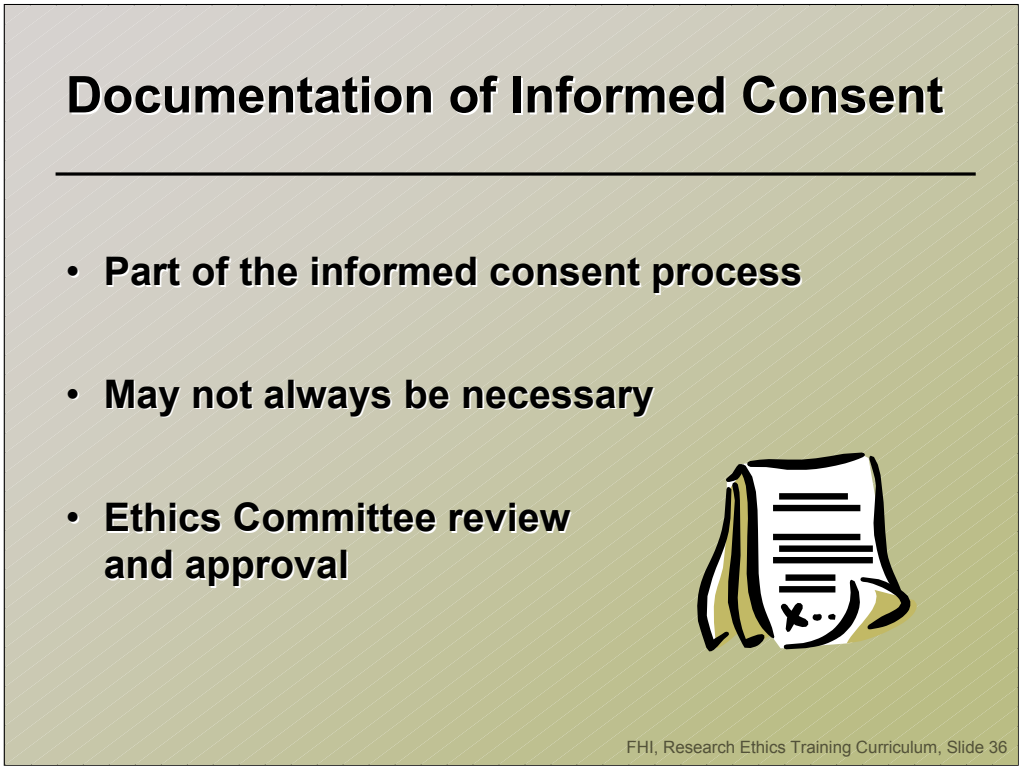
Information must be provided on whom to contact in case of questions related to injuries or rights. The contact should not be the researcher or any other person directly related to research. A member of the ethics committee may be an appropriate contact person.

The contact information that is provided to the participant should be realistic, economically viable and culturally appropriate.

Slide 35. Voluntary Participation

In the informed consent form, it is necessary to state that **participation is absolutely voluntary**. This chapter of the informed consent should indicate that refusal to participate in the research or the desire to withdraw from the study will not result in any penalties or loss of benefits to which the participant is otherwise entitled.

Learner Note: Can you think of any factors that might limit participant understanding that the research is absolutely voluntary?

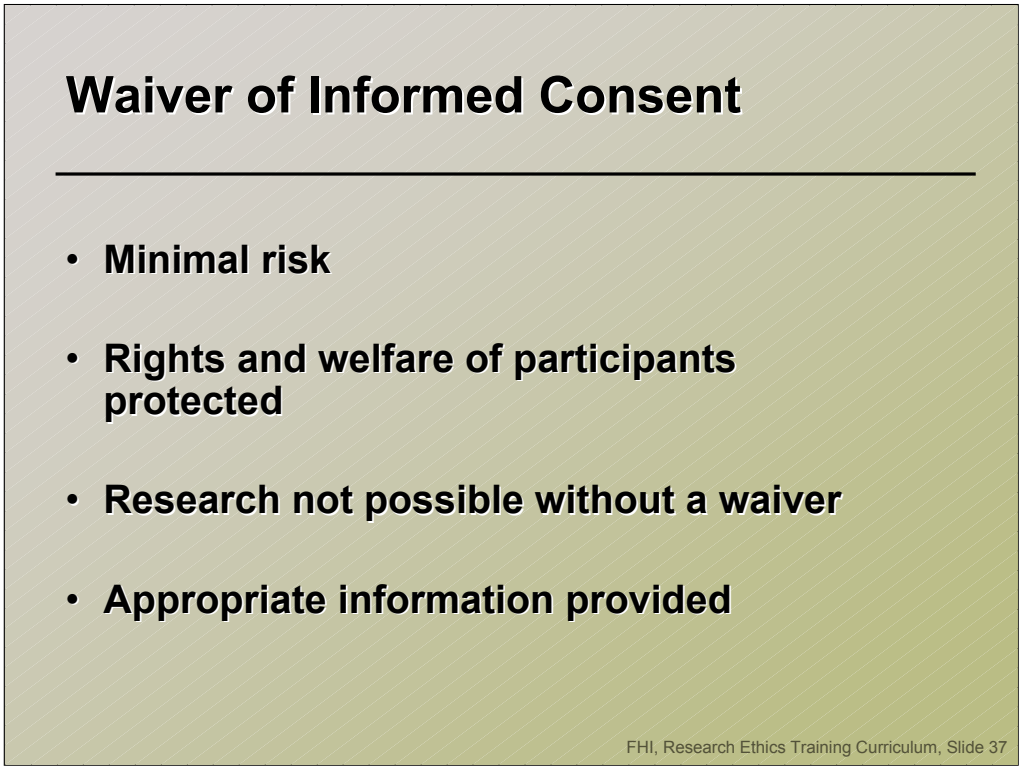


Slide 36. Documentation of Informed Consent

The informed consent form is commonly used to facilitate and standardize the process of informed consent. However, **a consent form itself does not constitute actual informed consent**; it is merely documentation. A key component to the process of informed consent is the signing, or documentation, of the consent form by the participant, the researcher and other individuals. All guidelines encourage written documentation when possible.

However, **a signature does not mean that the participant has understood** and given voluntary consent. The *Declaration of Helsinki* indicates that "after ensuring that the participant has understood the information, the physician should then obtain the participant's freely given informed consent, preferably in writing."

It is important to realize that the value of documentation will vary according to the specifics of the research and the setting of the research. Low-risk survey research may not require the participant's signature, and in some locations, participants may be uncomfortable signing forms. The ethics committee responsible for the study should determine and approve the method of documenting, or not documenting, informed consent.



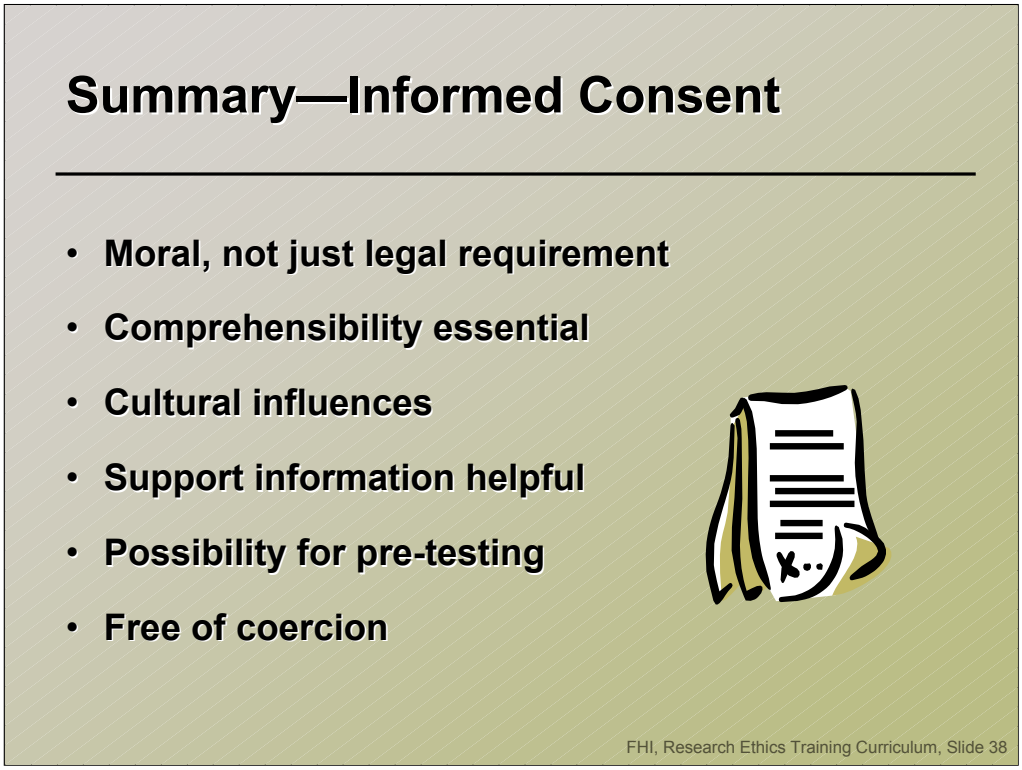
Slide 37. Waiver of Informed Consent

Although it is ideal to have an informed consent document that contains all recommended elements, there may be situations where this is not appropriate for the research. For some types of research, such as anonymous survey methods, some of the elements may not apply. In such cases, the local ethics committee may allow a waiver of informed consent that allows the researcher to delete some or all of the required elements.

The Common Rule provides 4 criteria for allowing a waiver:

- Research should involve no more than minimal risk to the participant.
- A waiver will not adversely affect the rights and welfare of the participants.
- The research could not be conducted without the waiver.
- When appropriate, the participants will receive additional pertinent information after their participation ends.

All requests for waivers should be submitted to the ethics committee before implementation of the research.



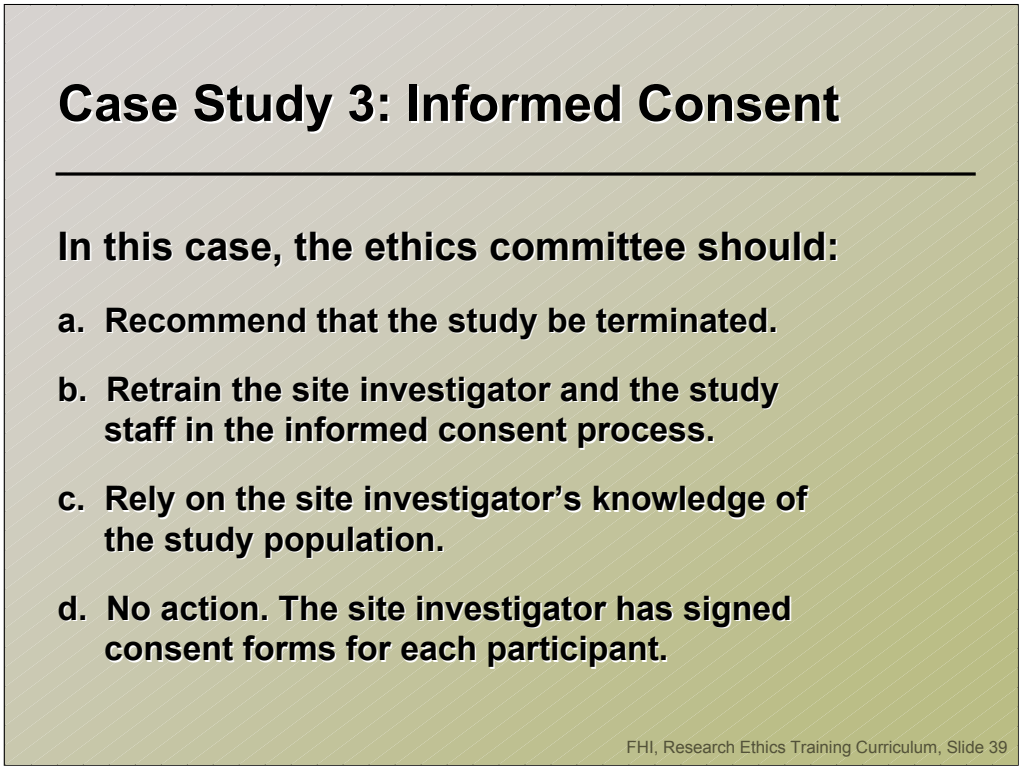
Slide 38. Summary—Informed Consent

Obtaining appropriate informed consent is necessary before any research is initiated. However, informed consent should not be seen as only a legal or regulatory requirement, but as **a moral obligation, designed to protect the basic human rights of research participants**.

Written documentation of informed consent is usually required. However, it is essential to ensure that the potential participant has understood all the information provided. The participant's education, maturity and cultural environment have a strong effect on one's ability to understand such information.

The challenge of informed consent is to provide sufficient information to make an informed decision, while at the same time presenting this **information in a manner that is comprehensible to the potential participant**. The use of support materials, such as brochures or videos should be considered. In studies where risks may be high, field-testing of the informed consent process should be considered prior to the study initiation.

Informed consent must be obtained without coercion or manipulation. **The researcher's special cultural or intellectual status should not play a role** in inducing the participant's decision. In some circumstances, informed consent may be better obtained by a neutral party without a direct interest in the research study. Vulnerable participants may require special protection.



Slide 39. Case Study 3: Informed Consent

A randomized placebo-controlled trial of a vaginal microbicide product is underway in a resource-poor country. The purpose of this trial is to look at the effectiveness of a topically applied microbicide on heterosexual acquisition of HIV. Half of the women enrolled will receive the test product and condoms and the other half will receive a placebo and condoms. Both the local ethics committee (EC) and sponsor's EC have approved this research and the consent process.

During a routine monitoring visit for this trial, the monitor observes the consent process for several study participants. The monitor finds that **the study counselors administering the informed consent do not explain all of the information on the consent form as was planned at the staff training.** In fact, most of the consent form is paraphrased and several essential elements are omitted. All participants sign the consent form.

When the counselors are questioned about this, **they state that the women at this site are not capable of understanding** everything in the consent form, so the site counselors and the study investigator agreed on emphasizing only the most important aspects of the consent form.

The monitor speaks to the investigator about this issue. She is told that investigators are encouraged to review and modify consent forms as necessary to account for local conditions. The investigator feels that the study counselors were correctly following the informed consent process. The monitor reports her findings to the EC.

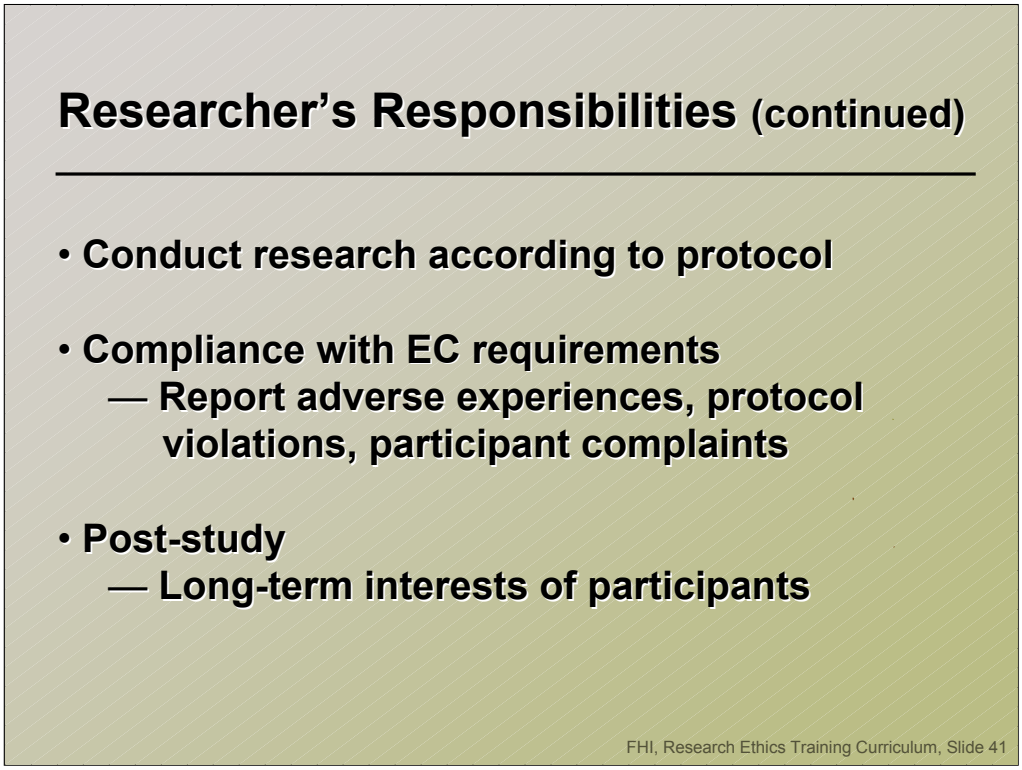
Learner Note: Make copies of this case study to hand out to small group participants so that they can follow the discussion.

Slide 40. Researcher's Responsibilities

Researchers have a number of responsibilities to ensure the protection of the people participating in research. These responsibilities are in response to legal requirements, but are also the **response to basic ethical norms that scientists and health care professionals must follow**. It is important to keep in mind that researchers may delegate some of the research work to other staff members. However, delegation does not relieve the researchers of any responsibilities. These responsibilities fall into the following main categories:

• Protection of human participants: The first level of responsibility is to develop scientifically and technically correct research protocols, **placing the welfare of participants above the interests of science and society**.

The Common Rule indicates that researchers "are responsible for ensuring that no human subject will be involved in the research before giving informed consent." The CIOMS guidelines also indicate that "the researcher has the duty to communicate to the prospective subject all the information necessary for adequately informed consent." Finally, the researcher has the obligation to protect the confidentiality of the participants as stipulated in the informed consent.



Slide 41. Researcher's Responsibilities (continued)

- Conduct research according to protocol: The researcher must conduct the study according to the approved protocol, and may **only make changes to the protocol with the approval of the EC.** The researcher is responsible for ensuring that **all staff are appropriately trained to conduct the research**. The researcher is also responsible for the authenticity of the data and the protection of all records.
- Compliance with EC requirements: The researcher must ensure that an EC will be responsible for the initial and continuing review and approval of the research and must provide the EC with all information necessary to perform these functions. Researchers are responsible for complying with all EC decisions, stipulations and recommendations. The researcher has the responsibility **to report to the EC any adverse event** that occurs in the conduct of the study, in accordance with regulations and EC requirements and to report to the EC any problems experienced in the conduct of the research, including protocol violations and any complaints from the research participants.
- Post-Study: Increasing **importance is now being given to the role and responsibilities of researchers once the study is concluded**. The NBAC report indicates that "the researcher's responsibilities include working to ensure local community access to benefits following the study."

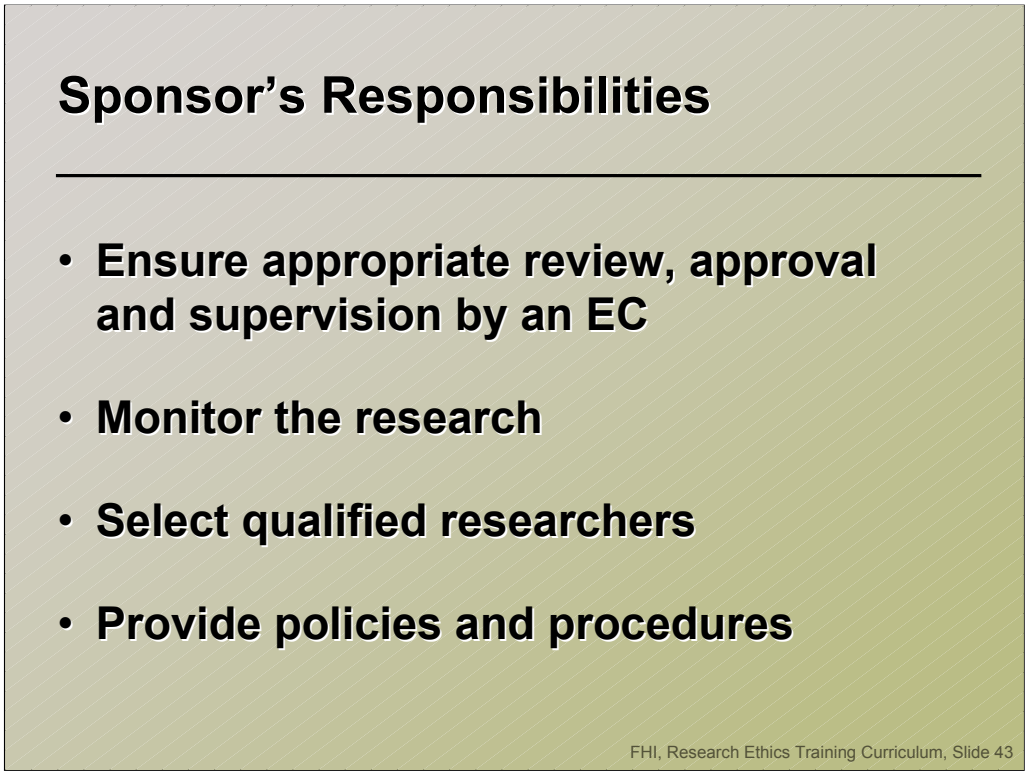
Slide 42. Researcher's Human Qualities

The Scientific Ethics program of the U.S. Centers for Disease Control and Prevention (CDC) states that, in addition to technical scientific responsibilities:

"The conduct of science requires a skillful and objective search for the truth in an atmosphere of honesty and trust."

Qualities that research staff should demonstrate to the research participants include:

- integrity
- respect
- compassion
- professionalism
- courtesy
- sensitivity



Slide 43. Sponsor's Responsibilities

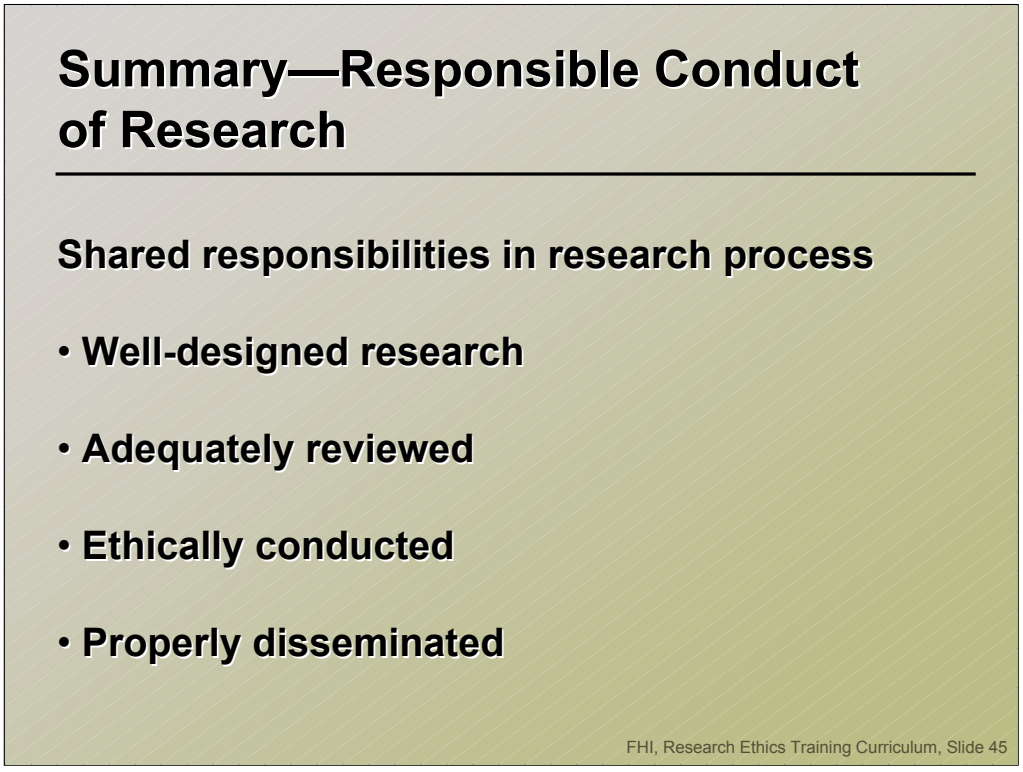
S**ponsors are responsible for providing an environment that promotes integrity, objectivity and the highest ethical standards of research**, including standards for design, implementation and reporting. Particularly, sponsors must commit to protect the participants in all research studies. Sponsors can accomplish these goals in several ways:

- **Support the establishment and operation of an appropriate ethics committee**, and ensure their review, approval and supervision of all research.
- **Monitor the research** according to a plan approved by the EC, ensuring that the study is conducted according to the approved protocol, and that all data are authentic, reliable and processed correctly.
- **Select** only **qualified researchers** and provide them with all the necessary means to implement the research properly.
- **Provide** all researchers with **written policies**, **procedures** and **guidelines** before the research is initiated.

Slide 44. Sponsor's Responsibilities in International Research

Additionally, in the case of international research, the sponsors must:

- Encourage review by a local EC and ensure that the proposed research **complies with the local** ethical, regulatory and legal **requirements**. Both the CIOMS guidelines and the NBAC report recommend that external sponsors provide financial, educational and other assistance to promote capacity-building in the area of local independent ethical review of research.
- Prior to study initiation, **discuss with local partners** the relevance of the research to the local needs and priorities and the potential benefits of such research for the participating communities. Once the research has ended, sponsors should also make reasonable efforts to make the products of the research available to the participants.
- Define policies and procedures for **promoting research integrity** and for dealing with allegations or evidence of scientific misconduct.

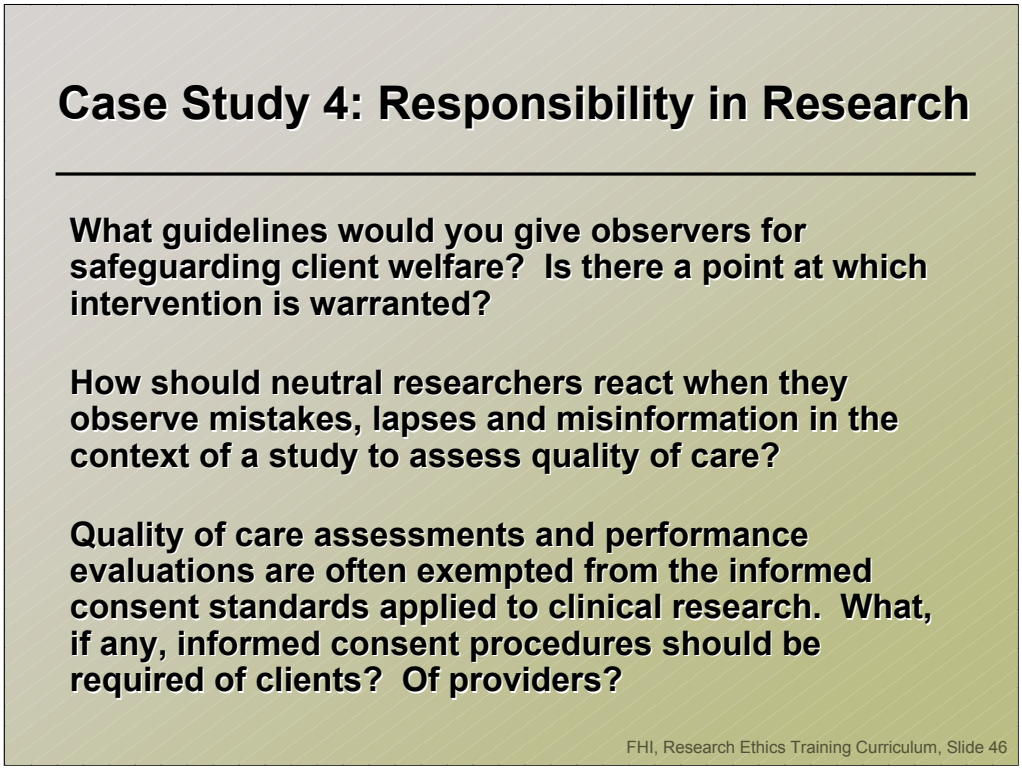


Slide 45. Summary—Responsible Conduct of Research

Sponsors and researchers share many responsibilities throughout the research process, primarily:

- designing ethical research that meets local need
- ensuring proper ethical review and approval of the research
- conducting the research according to the highest ethical standards
- applying and sharing the knowledge gained by the research

By embracing these responsibilities, sponsors and researchers adhere to both the rules of research and the rules of society.

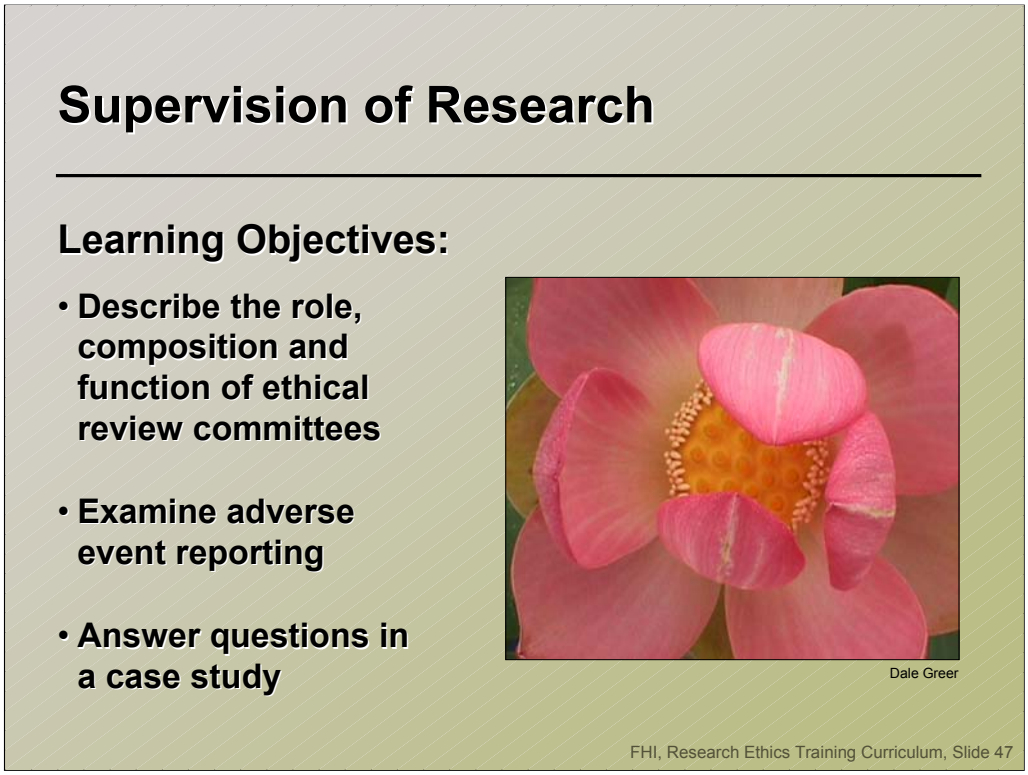


Slide 46. Case Study 4: Responsibility in Research

A local consultant has been hired by an international reproductive health research organization to conduct research on family planning service delivery. Her job is to design and manage a clinic-based study to measure standard indicators of quality of care. She realizes that a critical component of the research will be observation of client—provider interactions.

With her intimate knowledge of the local health system, the consultant realizes that the observers she must hire and train will need to strike a balance between neutral observation and advocacy for client welfare. In fact, during the pre-test of the observation data collection instrument, **she observed many instances of poor-quality care.** For example, some providers failed to mention side effects of the clients' chosen family planning method or they answered clients' questions erroneously. She did not intervene in these situations. However, she began to worry about how her observers should handle more serious problems they might witness, such as providers' failure to wash their hands between pelvic exams or before insertion of an IUD.

Learner Note: Make copies of this case study to hand out to small group participants so that they can follow the discussion.



Slide 47. Supervision of Research

The learning objectives for the Supervision of Research are:

- Describe the role, composition and function of ethical review committees
- Examine adverse event reporting
- Answer questions in a case study

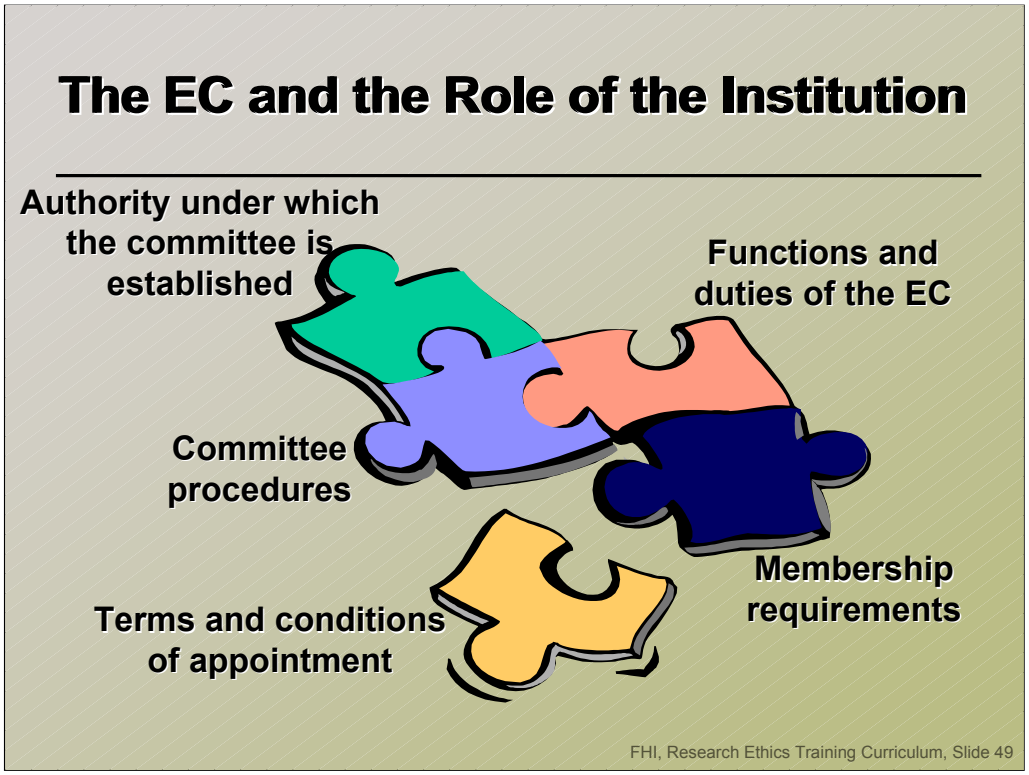
Slide 48. Research Supervision: Ethics Committees

An integral component of the responsible conduct of research is **supervision of the research**. Most current regulations and guidelines **require review and approval by independent ECs.**

Ethics committees exist under a variety of titles, including Research Ethics Committee, Institutional Review Board, Ethics Review Committee, Ethics Review Board, and countless others. The World Health Organization (WHO) refers to these groups as ethics committees (ECs)—this is the term used in this curriculum.

Regardless of the name, the committee's responsibility is to **review research to ensure the protection of human participants.**

Learner Note: The full text of the WHO *Operational Guidelines for Ethics Committees That Review Biomedical Research* is included in the *References* section of the curriculum.



Slide 49. The Ethics Committee and the Role of the Institution

Institutions that conduct research with human participants are responsible for the ethical review of the research. To do this effectively, institutions should create operational guidelines to guide the work of the EC. WHO recommends that operational guidelines include:

- the authority under which the committee is established
- the functions and duties of the EC
- membership requirements
- the terms and conditions of appointment
- committee procedures

The development of guidelines is not sufficient. To be effective, the institution must designate **sufficient resources** to support the ongoing operations of the committee. In addition, the institution must demonstrate to research staff that the EC is an important part of the research program.

Slide 50. Ethics Committee Members

ECs responsible for the review of research involving human participants must be properly qualified to:

- assess the research
- represent the interests of the community where the research will be conducted

This is achieved through the **careful selection of members**.

Learner Note: List criteria to consider when selecting EC members.

Slide 51. Ethics Committee Membership

WHO guidelines and *The Common Rule* offer guidance for the selection of committee members. Both agree that EC membership should have the following characteristics:

- **relevant scientific expertise or other specialized knowledge**. Members should be qualified to review specific research activities as well as the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice.

- **nonscientific representatives from the community**. It is important that people from the community where research is to be conducted have a voice representing their culture, interests and concerns. These members must be accorded the same level of respect as their scientific counterparts.

- **diversity of sex, age and cultural background of members**. Diversity will promote a balanced review of the research.

In addition, the EC should have access to nonvoting consultants with specialized knowledge when needed.

Slide 52. Ethics Committees: Criteria for Review and Approval

In order to approve a research project, the EC must examine the proposed research thoroughly. At a minimum, the **EC should address 6 core issues**:

- **scientific design and conduct of the study**. The EC should consider the design of the research to the extent that it impacts the safety of the participants.

  Are procedures consistent with appropriate research design?

  Is the researcher qualified to conduct the research?

  It is recommended that the research be reviewed by a scientific review committee prior to EC submission. The scientific committee reviews the technical or scientific aspects of the study.

- **recruitment of research participants**. The EC should examine the materials and methods by which participants will be recruited.

  Are the recruitment methods appropriate for the research setting and the subject population?

  Are there appropriate safeguards in place to protect vulnerable populations?

- **community considerations**. The research should address a local need or problem and must be designed with an understanding of the community in which a study will take place. The EC must assess the impact of the research on the community.

  How will the community benefit from the research?

  How will community members be included in the design of the study?

Slide 53. Ethics Committees: Criteria for Review and Approval (continued)

- **care and protection of research participants**. The EC must examine the impact of the research on the participants.

  Are adequate measures in place to provide for the well-being of the participant during and, if appropriate, after the study?

  How is the study being monitored to ensure the safety of research participants?

- **informed consent**. All codes and guidelines require individual informed consent.

  Are participants adequately informed about the study, the voluntary nature of their participation, and their right to end their participation at any time?

  How is informed consent documented?

- **confidentiality issues**. The EC must review the steps taken by the research team to protect the confidentiality of participants. In some research, the greatest risk could well be a breach of that confidentiality.

  Are adequate measures in place to protect confidentiality?

  Will participants be at risk if confidentiality is broken?

Only when all these questions have been answered should the EC grant approval.

Slide 54. Ethics Committees: Post-approval Role

The work of the EC does not end when approval is granted for a research study. Because research studies often evolve during their development and implementation, it is important that ECs are aware of these changes and agree that the changes do not affect their original decision to approve.

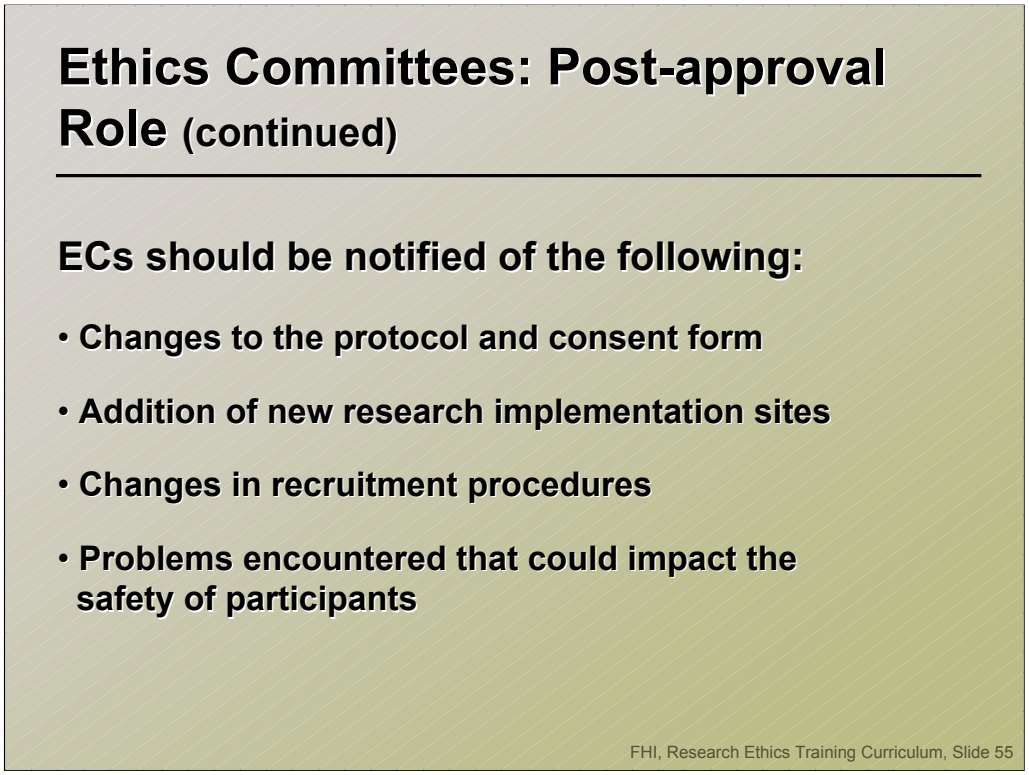
Learner Note: List 4 items that must be submitted to the EC for review after initial approval.

1. For example—changes to the consent form or protocol

2.

3.

4.

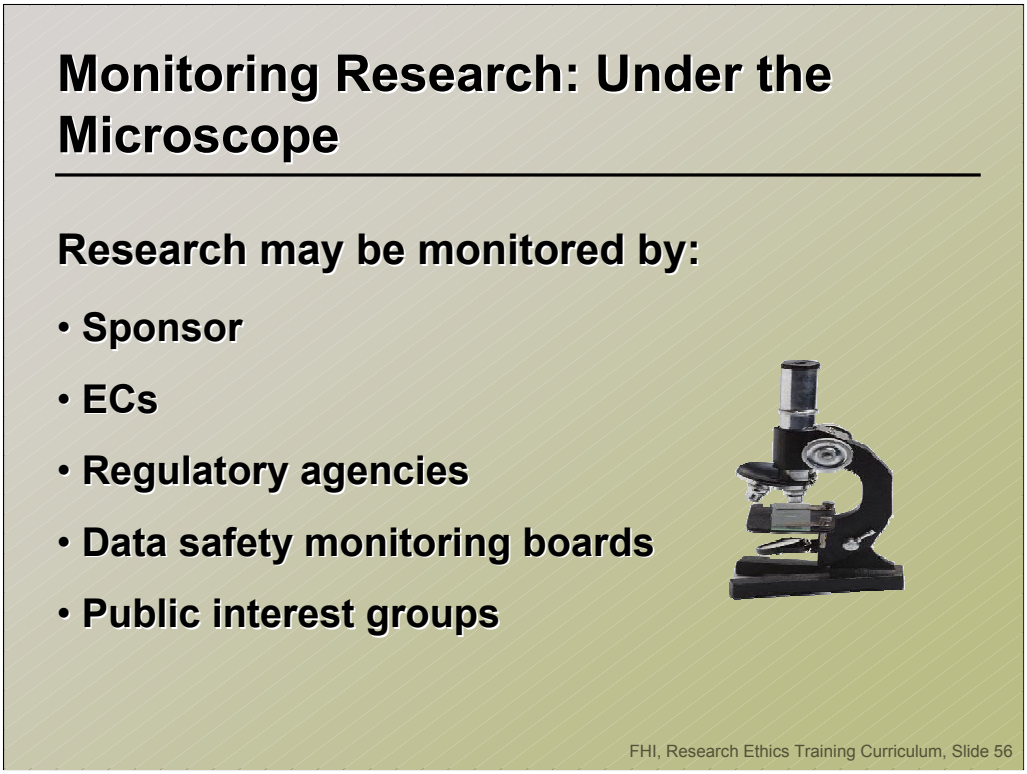


Slide 55. Ethics Committees: Post-approval Role (continued)

After initial protocol approval, the following should always be submitted to the EC for review:

- **Changes** to the **protocol** and **consent form**
- **Additions** of new research implementation sites
- **Changes in recruitment procedures**, including advertising and informed consent
- **Problems encountered** in the course of the research that could impact the safety of participants or their willingness to continue in the research

It is recommended that status reports for research studies be reviewed at least annually by the EC. These reports contain information on the conduct of the study and any problems encountered to date. Each EC will have its own specific procedures and requirements for continuing review.



Slide 56. Monitoring Research: Under the Microscope

In addition to the initial review requirements, **research** that is ongoing is **subject to monitoring from several different groups**. These groups can include the sponsor of the research, contracted monitoring organizations, regulatory agencies, and institutional committees such as the EC. Monitoring may consider issues related to the **safety of participants as well as laboratory and other facilities, study records, other documentation, or any combination of the above**. Sponsors, regulatory agencies and ECs have the power to suspend research studies.

Multisite clinical trials, particularly Phase II and Phase III trials, may be monitored by data and safety monitoring boards (DSMBs). The DSMB's role is to review the progress of the study, with access to interim analyses and adverse event reports. DSMBs operate according to a strict plan that includes criteria for ending a research study while in progress.

In addition to the various groups that will officially monitor a study, researchers should be aware that **unofficial monitoring** may occur by the media or other concerned citizen groups. Careful design, review, and conduct of a study can help protect against negative public opinion.

Slide 57. Adverse Event Reporting

Unfortunately, **some research participants will experience an adverse event.**

The ICH defines 2 categories of adverse events:

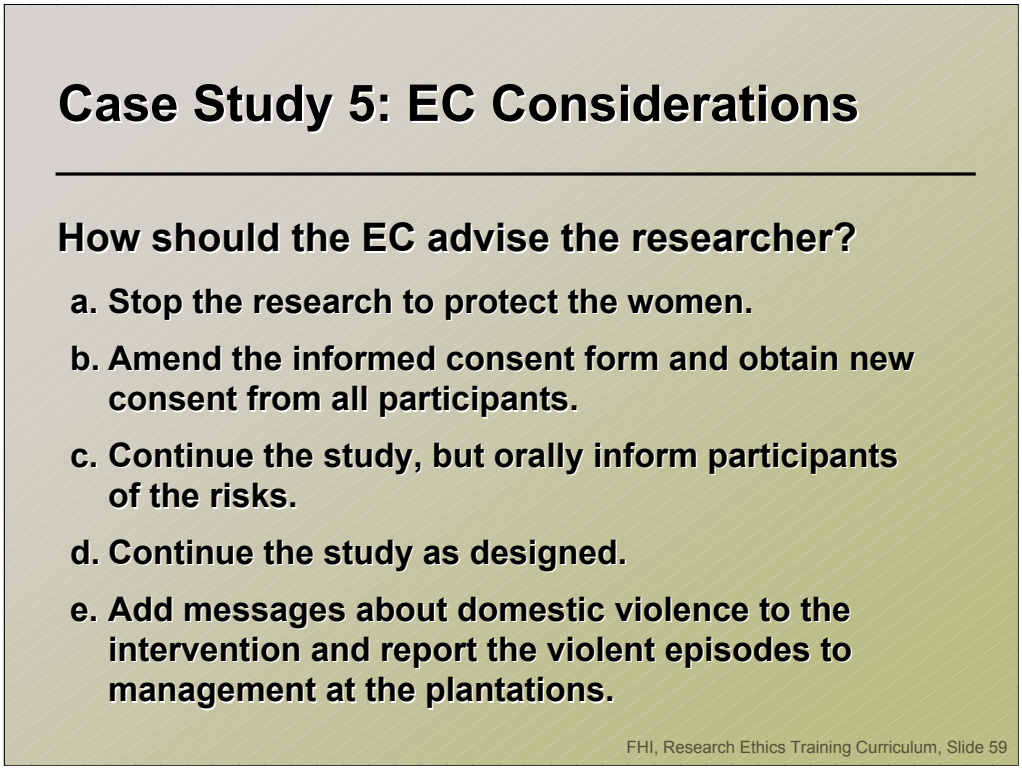
- Adverse Event (AE): "any untoward medical occurrence in a research participant which does not necessarily have a causal relationship with the research intervention."
- Serious Adverse Event (SAE): "any untoward medical occurrence that: results in death; is life-threatening; requires hospitalization or prolongs existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect."

SAEs are classified as either **related** or **unrelated** to the study intervention. Those that are related to the research may require a more thorough investigation. Also, many medical procedures involve a known risk. In other words, the procedure is likely to result in a SAE, but it is **expected.** The researcher should be prepared for **unexpected** SAEs.

Many ECs have specific reporting requirements regarding adverse events. A high number of unexpected or related SAEs may cause the EC to suspend a study pending a special review. **Most study protocols should have guidelines for documenting and reporting adverse events**.

Slide 58. Summary—Supervision of Research

A well-trained, active and objective EC is very important to research that involves human participants. Given the complex nature of research, a **thorough and thoughtful review by the EC** will allow the researcher to conduct the best possible study while protecting the rights and the welfare of human research participants.



Slide 59. Case Study 5: EC Considerations

A cluster-randomized trial is conducted at rural plantations in a developing country. The study sites, rather tha the individual study participants, are randomly selected to receive the intervention or not. **Intervention sites introduce female condoms along with continued distribution of male condoms**, while the **control sites receive male condoms only**. All adult male and female residents of the sites are exposed to the intervention b means of large entertainment events featuring music, dance and puppetry.

The participants are women who undergo screening and informed consent, and are then interviewed and tested for sexually transmitted infections (STIs) at each of 3 follow-up visits over the course of 12 months. **The informed consent form mentions the strain and distress that can accompany a diagnosis of STI, with no reference to the possibility of more serious, perhaps violent repercussions.**

Despite the informational program, one percent of the women report trauma as a result of abusive behavior by their sexual partners. As documented on *Serious Adverse Event* forms, women are assaulted for:

- informing partners of study participation
- suggesting condom use to partners
- notifying partners of STI-positive status and asking partners to seek treatment

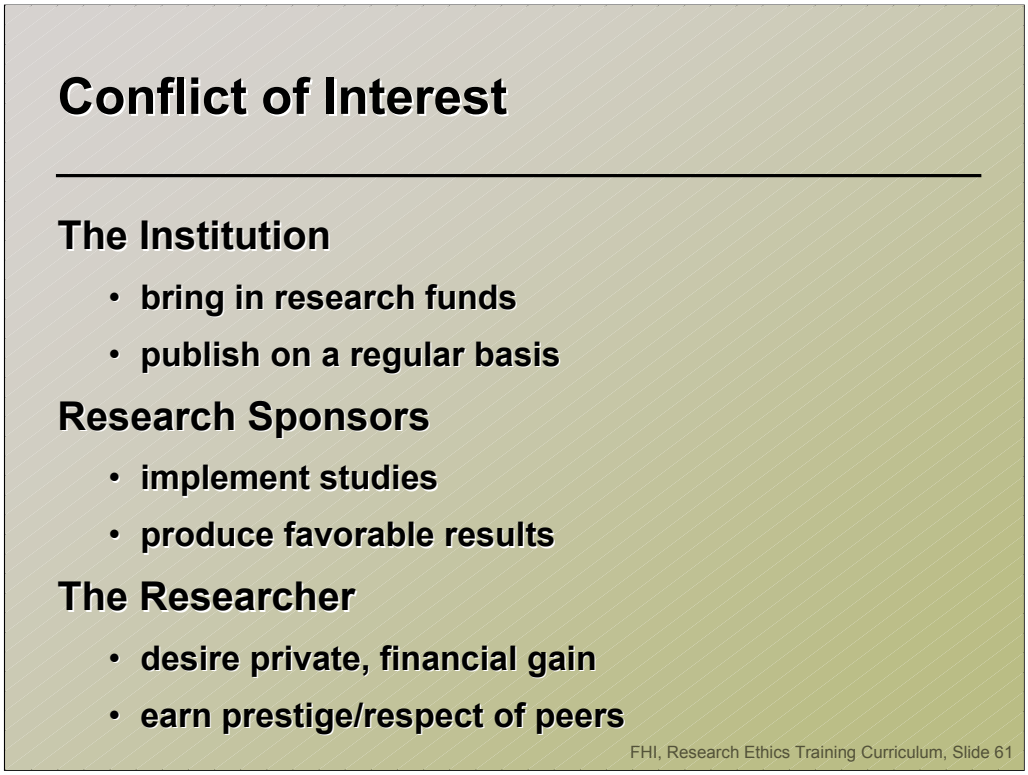
It is understood that this partner violence is a direct result of participating in this study. Violent incident are reported to service providers at both intervention and control sites. This is the only problem reported in th research study thus far.

Learner Note: Make copies of this case study to hand out to small group participants so that they can follow the discussion.

Slide 60. Special Issues in Research

The learning objective for Special Issues is:

- Examine conflict of interest and scientific misconduct

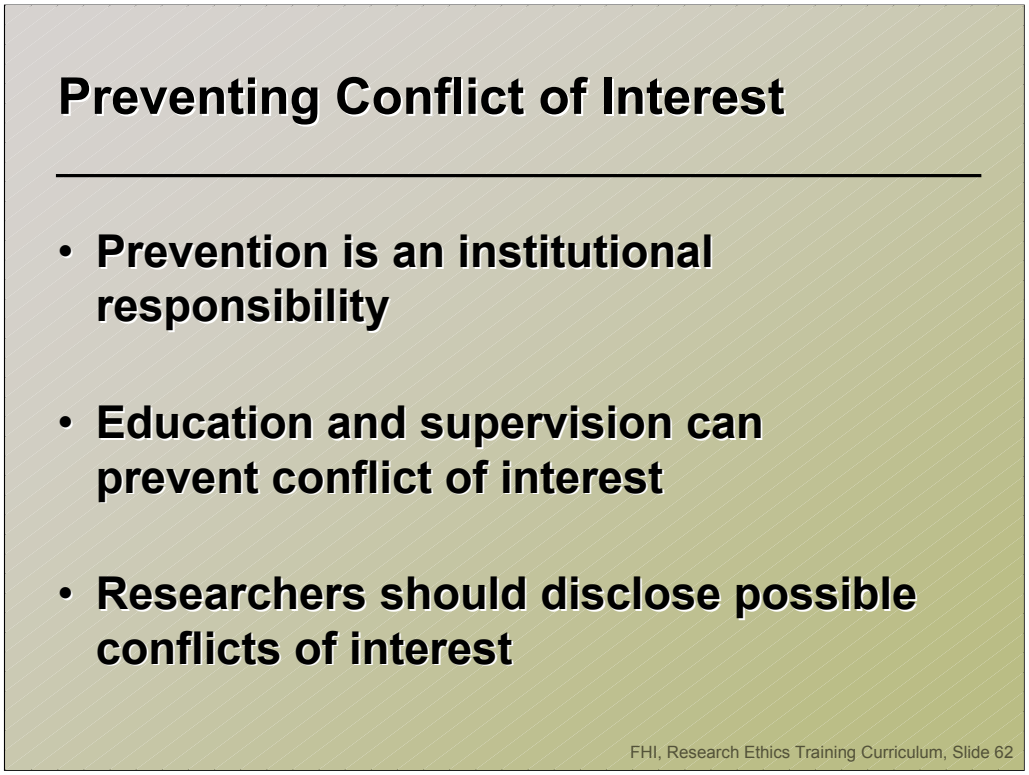


Slide 61. Conflict of Interest

The current **research environment is one of high expectations and high pressure**. The sources of potential pressure include:

- **the institution**. Researchers are required to **publish** in peer-reviewed journals on a regular basis and to **help raise money** through grants and contracts. This is in addition to routine teaching, clinical and laboratory responsibilities.
- **research sponsors**. A sponsor that awards a grant or contract to a researcher often expects the researcher to work only on that project. In addition, many sponsors are also eager for **favorable results**.
- **the researcher**. Researchers often desire the **respect of peers**. This can often be accomplished through successful research. In addition, the researcher may be motivated by a desire for personal financial gain for himself, family members or business partners.

If present, these demands may contribute to a conflict of interest that can lead to potential scientific misconduct on the part of the researcher.

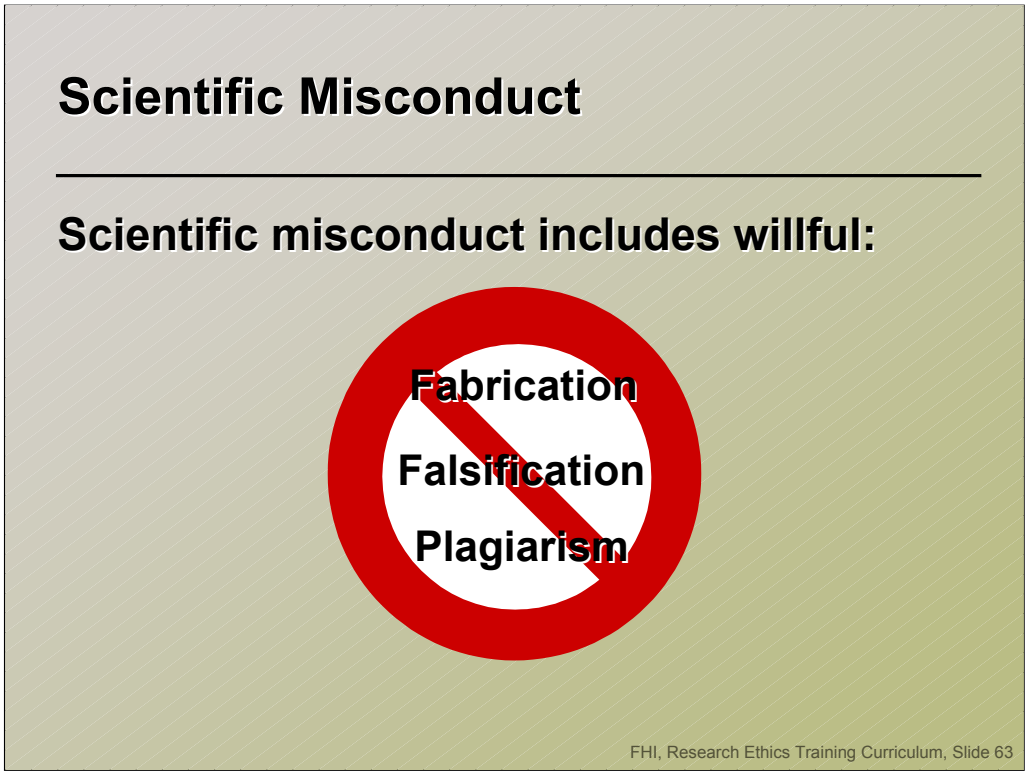


Slide 62. Preventing Conflict of Interest

The institution should take steps to minimize conflict of interest. This can be accomplished through **education of the research staff and proper supervision** of the research. Many institutions now require that researchers disclose conflicts of interest, with conflict of interest committees reviewing and, when required, developing a strategy for managing the conflict.

In addition, many journals require that the researchers disclose possible conflicts of interest when submitting articles for publication.

Learner Note: List examples of conflicts of interest that you have heard about. Discuss how they could have been avoided or resolved.

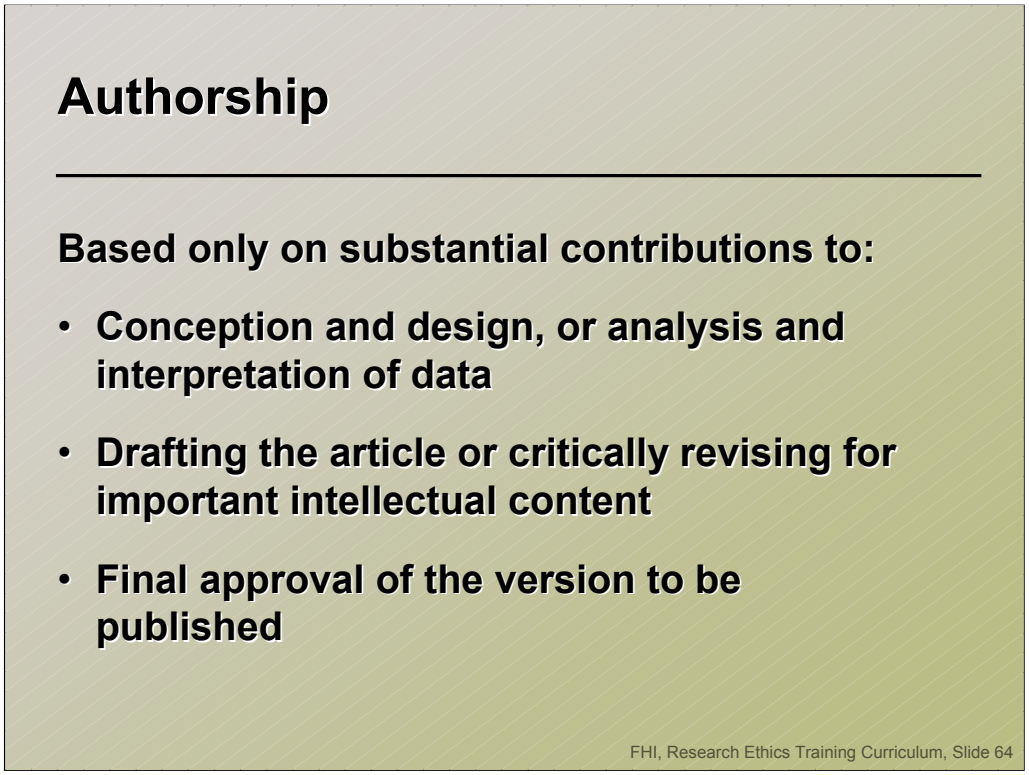


Slide 63. Scientific Misconduct

Scientific misconduct includes fabrication, falsification, plagiarism, or other practices that deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research.

Scientific misconduct does not include honest error or honest differences in interpretations or judgments of data.

All employees or individuals associated with the institution should report observed, suspected or apparent misconduct to the appropriate institutional official without fear of retaliation.



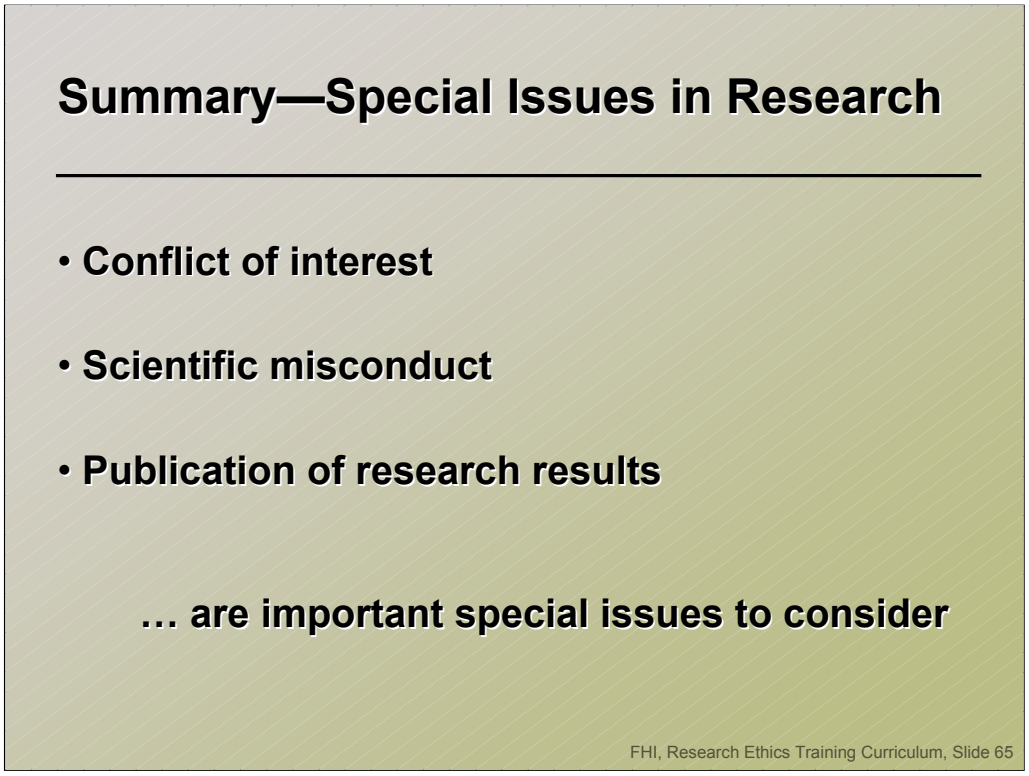
Slide 64. Authorship

One of the goals of research is to obtain generalizable knowledge. One means of disseminating generalizable knowledge is through publication.

Publication takes place once the study has been completed, and all data has been collected and appropriately analyzed and contributes to the use of research results. Researchers may find themselves under pressure to publish because of personal goals or institutional demands. Care must be taken to avoid fragmentation or any type of unnecessary duplication of publications.

In any publication, all persons designated as authors should qualify for authorship. According to the International Committee of Medical Journal Editors, "authorship should be based only on substantial contributions to:

- conception and design, or analysis and interpretation of data
- drafting the article or revising critically for important intellectual content
- final approval of the version to be published."



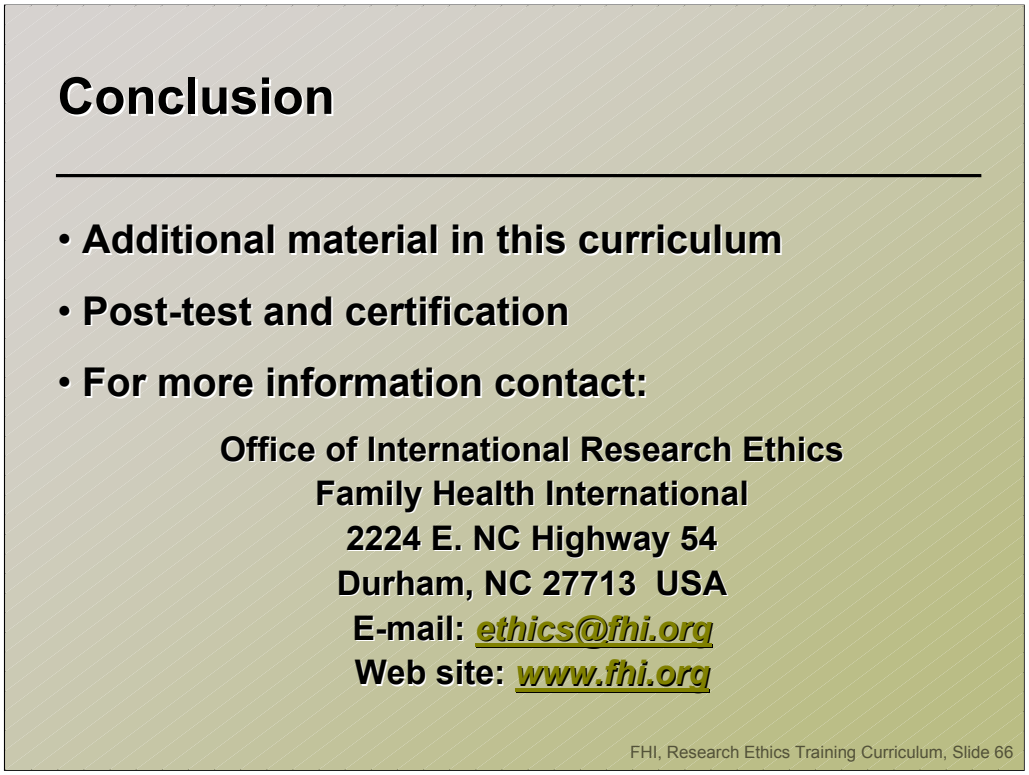
Slide 65. Summary—Special Issues in Research

Many special issues exist when conducting and reporting on research that involves human participants.

It is important to recognize the role and possible effects on research of:

- conflict of interest
- scientific misconduct
- publication of research results

By actively considering special issues, researchers will be better equipped to prevent tainting the research results.



Slide 66. Conclusion

We hope that you will take the messages of this curriculum with you as you return to your colleagues in the field and your research endeavors. Additionally, we hope that your interest in research ethics does not end with this curriculum. To that end, we encourage you to review the following materials included with this curriculum. Please review:

- additional case studies
- copies of key reference documents
- a list of Internet resources
- a selected bibliography

Please take time now to complete the post-test. Once your post-test is completed, you may obtain a certificate of completion from FHI. Instructions on how to obtain your certificate are at the beginning of the *Evaluation* section.

Learner Note: If you are a presenter, you should prepare a flip-chart with your local contact information.

Case Studies

Family Health International

Case Studies Guidelines

Note to the Presenter

The *Case Study* section provides 8 reproductive health case studies to prompt thoughts about the material presented in the curriculum.

Case Study 1: Respect for Persons (slide 6)
Case Study 2: Beneficence and Justice (slide 9)
Case Study 3: Informed Consent (slide 38)
Case Study 4: Responsibility in Research (slide 45)
Case Study 5: EC Considerations (slide 58)

Additional Case Studies
Case Study 6: Negative Media Coverage
Case Study 7: Research with Minors
Case Study 8: Conflict of Interest

The following 8 case studies reflect actual research study situations. In most cases, you may not find right or wrong answers to the questions. Both text and questions may show flaws in their design; however, they were written this way to prompt discussion.

The case studies will elicit a variety of reactions. While they are focused in the area of reproductive health research, the issues that are raised transcend one specific category of research, and they were written to raise a multitude of discussions and considerations. This type of discussion will enrich the working group and should be pursued; however, the training leader may need to curtail some discussions in the interest of time.

The case studies illustrate the complexity of human research and how cultural, social and gender issues impact the ethics of a research study.

We believe that these case studies are applicable to most settings, but the discussions of characteristics that are unique to a particular country are encouraged.

Case Study 1: Respect for Persons

A local Ministry of Health has requested a prevalence/behavioral surveillance study for sexually transmitted infection (STI) among commercial sex workers. Participants in this study will be tested for 3 common STIs and participate in an interview. Participants will receive a card with a number linking them to their blood sample. Women who donate blood will have the option of presenting their card to get the results of the STI tests. Those with positive results for any of the 3 infections will be offered free treatment. In addition, all participants will receive a small gift in return for their participation.

The target population consists of brothel-based sex workers who are strictly controlled by the brothel managers. Prior to initiating the research, the researcher meets with the brothel manager to ask permission to conduct the study. During the meeting, **the manager states that all of the women working in the brothel will participate in the study.**

Questions:

1. What steps can the research staff take to ensure that the informed consent is freely given by all participants?

2. If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager?

3. If you believe that the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health?

Case Study 2: Beneficence and Justice

A time-series intervention trial was conducted with commercial sex workers. **The goal of the trial was to assess the impact of adding the female condom to a male condom distribution system, measured in terms of a change in the proportion of sex acts protected by condoms.** Condom use was estimated by interviewing study participants about their use of protection in their last 10 sex acts. These measurements were to be made at 5 time points: twice following exposure to male condom promotion and distribution activities, and 3 times following promotion and distribution of both the male and female condom.

The local principal investigator, a highly respected advocate for the sex workers, explained that women were very enthusiastic about participating in the female condom trial, as it would provide them free access to this innovative method of dual protection.

The first round of condom use measurement was completed as planned. Preliminary data analysis revealed that study participants were reporting male condom use in over 95% of sex acts. Following verification of the interviewers' techniques, a second round of interviews was completed. It yielded a similar, exceptionally high-level of male condom use. **There is concern that introducing a new product will have a negative affect on the use of male condoms. In addition, there are questions about the availability and affordability of the female condoms after the conclusion of the study, even if the study is successful.**

Question:

What is the best way to proceed?

a. Continue the study as designed.

b. Terminate the study.

c. Suspend the study. Seek assurance that female condoms will be made available if proved successful.

Case Study 3: Informed Consent

A randomized placebo-controlled trial of a vaginal microbicide product is underway in a resource-poor country. The purpose of this trial is to look at the effectiveness of a topically applied microbicide on heterosexual acquisition of HIV. Half of the women enrolled will receive the test product and condoms and the other half will receive a placebo and condoms. Both the local ethics committee (EC) and sponsor's EC have approved this research and the consent process.

During a routine monitoring visit for this trial, the monitor observes the consent process for several study participants. The monitor finds that **the study counselors administering the informed consent do not explain all of the information on the consent form as was planned at the staff training.** In fact, most of the consent form is paraphrased and several essential elements are omitted. All participants sign the consent form.

When the counselors are questioned about this, **they state that the women at this site are not capable of understanding** everything in the consent form, so the site counselors and the study investigator agreed on emphasizing only the most important aspects of the consent form.

The monitor speaks to the investigator about this issue. She is told that investigators are encouraged to review and modify consent forms as necessary to account for local conditions. The investigator feels that the study counselors were correctly following the informed consent process. The monitor reports her findings to the EC.

Question:

In this case the ethics committee should:

a. Recommend that the study be terminated.

b. Retrain the site investigator and the study staff in the informed consent process.

c. Rely on the site investigator's knowledge of the study population

d. No action. The site investigator has signed consent forms for each participant.

Case Study 4: Responsibility in Research

A local consultant has been hired by an international reproductive health research organization to conduct research on family planning service delivery. Her job is to design and manage a clinic-based study to measure standard indicators of quality of care. She realizes that a critical component of the research will be observation of client-provider interactions.

With her intimate knowledge of the local health system, the consultant realizes that the observers she must hire and train will need to strike a balance between neutral observation and advocacy for client welfare. In fact, during the pre-test of the observation data collection instrument, **she observed many instances of poor-quality care.** For example, some providers failed to mention side effects of the clients' chosen method or they answered clients' questions erroneously. She did not intervene in these situations. However, she began to worry about how her observers should handle more serious problems they might witness, such as providers' failure to wash their hands between pelvic exams or before insertion of an IUD.

Questions:

1. What guidelines would you give observers for safeguarding client welfare? Is there a point at which intervention is warranted?

2. How should neutral researchers react when they observe mistakes, lapses, and misinformation in the context of a study to assess quality of care?

3. Quality of care assessments and performance evaluations are often exempted from the informed consent standards applied to clinical research. What, if any, informed consent procedures should be required of clients? Of providers?

Case Study 5: EC Considerations

A cluster-randomized trial is conducted at rural plantations in a developing country. The study sites, rather than the individual study participants, are randomly selected to receive the intervention or not. **Intervention sites introduce female condoms along with continued distribution of male condoms**, while the **control sites receive male condoms only**. All adult male and female residents of the sites are exposed to the intervention by means of large entertainment events featuring music, dance and puppetry.

The participants are women who undergo screening and informed consent, and are then interviewed and tested for Sexually Transmitted Infections (STIs) at each of three follow-up visits over the course of 12 months. **The informed consent form mentions the strain and distress that can accompany a diagnosis of STI, with no reference to the possibility of more serious, perhaps violent repercussions.**
Despite the informational program, one percent of the women report trauma as a result of abusive behavior by their sexual partners. As documented on *Serious Adverse Event* forms, women are assaulted for:
• informing partners of study participation
• suggesting condom use to partners
• notifying partners of STI-positive status and asking partners to seek treatment

It is understood that this partner violence is a direct result of participating in this study. Violent incidents are reported to service providers at both intervention and control sites. This is the only problem reported in the research study thus far.

Question:

How should the ethics committee advise the researcher?

a. Stop the research to protect the women.

b. Amend the informed consent form and re-consent all participants.

c. Continue the study, but orally inform participants of the risks.

d. Continue the study as designed.

e. Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.

Case Study 6: Negative Media Coverage

Nonoxyl-9 (N-9), a widely used spermicide, has been on the market for 50 years with an excellent safety record for its intended indication. The product has been found to be effective in vitro against a number of important pathogens for which it was not originally intended. Numerous clinical trials with N-9 are being conducted to show effectiveness in preventing infection by the new pathogens, some of which lead to death.

At a large international conference, preliminary analysis from interim data results are presented on a randomized phase III trial comparing N-9 to a similar product. The study results show that **the group of women using the test product had a higher incidence rate of HIV infection than the group using the comparison product**. There is a general call from the media, international health organizations and leading U.S. health organizations to halt all ongoing and planned clinical trials using N-9 and inform all women in these trials that they may be at increased risk of contracting the deadly infection. You are currently conducting a study to test N-9. However, your participant population is very different from the population enrolled in the trial that produced the results.

Questions:

1. Would you continue your research study?

a. No, there is no justification for putting women at risk.

b. Proceed with ongoing research.

c. Proceed with planned and ongoing research, but increase safety surveillance.

2. Should women who are enrolled in your research be informed of the data announced at the international conference?

a. Yes; they deserve to know.

b. No; it would create unnecessary fear and confusion.

Case Study 7: Research with Minors

A new sexuality education curriculum (also called family life education or FLE) is being tested in 10 middle schools. As part of the evaluation, a survey will be administered to a sample of classes in 10 schools that have implemented the FLE curriculum and in 10 classes in schools using the old curriculum. The survey will be administered before the curriculum is implemented and again after the school year is over. Data from baseline and end-of-project surveys will be linked for each participant. The average age of the students in these classes is 13 years. Students will be asked about drug use, sexual experience, sexually transmitted infection knowledge, etc.

Sexuality education has been taught in these schools before, but the curriculum being tested uses an innovative teaching methodology. The country is culturally very conservative and sexual issues are not usually openly discussed. Schools in this country do not usually require parental consent for any kind of data collection or evaluation of curricula. Principals and teachers at the schools have told researchers that it will be very difficult to get written parental consent and that they would prefer not to try. Difficulties in getting consent are not related to parents' disapproval of their children's participation, but rather a general lack of involvement in students' school life in general and the students' difficulty in getting papers signed and returned. Many children do not even live with their own parents.

Questions:

1. **Given the country s conservative culture, should parental permission be sought for this study?**

    a. The research takes place in the schools. School officials should decide matters of parental permission.

    b. No; the participants are over 12 years old.

    c. Yes; parents have a right to know what their children are being taught, particularly concerning issues related to sexuality.

    d. No; obtaining parental permission may bias the answers that students provide.

2. **If it is determined that parental permission is not required, what mechanisms could be incorporated to ensure that students participate voluntarily and to protect them from peer pressure, discrimination by teachers, etc?**

    a. A teacher-parent advisory committee could be formed to review the study procedure in order to provide feedback to the researchers about concerns for the children involved in the study.

b. A parent from each class could be asked to be present during the survey administration.

c. Information about the survey is sent home to parents.

d. Informed consent could be obtained privately from each individual.

Case Study 8: Conflict of Interest

An urban church-run health center is a popular alternative for many people who complain about the poor services and lack of confidentiality in the public-run clinics. As a researcher investigating the effects of a new post-test HIV counseling and case management program, the church health center seems like a perfect site. The well-trained staff of the health center is interested in your research and has past experience implementing similar research with other diseases. The center is already the preferred HIV-testing site in the city.

Upon further discussions with the health center staff, you learn that they are not willing to distribute condoms to post-test clients, even those who test positive for HIV. Although your study does not require condoms to be distributed, you are alarmed that the center would refuse to distribute condoms to HIV-positive clients, thus putting their partners at risk of HIV.

Questions:

1. Do you continue to include this health center in your study?

2. Are there effective alternatives to providing condoms to infected participants?

3. The trial does not depend upon the provision of condoms and could still be conducted. Do you have a moral obligation to the participants?

Case Studies Answer Key

Case Study 1: Respect for Persons

Question 1: What steps can the research staff take to ensure that the informed consent is freely given by all participants?

First, the researcher should work to educate the brothel manager. Informing him that nonparticipation is acceptable to you may cause him to relax his attitude. In addition, the informed consent process should take place in a private, confidential setting. Women should be reminded repeatedly of the voluntary nature of the research.

Question 2: If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager?

Because the manager may insist that women participate, it will be imperative that nonparticipants are anonymous. Conducting informed consent individually will be important so that peer pressure is reduced. In addition, one might consider treating all of the women as if they had enrolled. (For example, giving nonparticipants thank-you gifts or fake blood sample cards will make it difficult to distinguish the participants from the nonparticipants.)

Question 3: If you believe that the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health?

If the target population will not be able to consent freely, then you are obligated to change the study or choose a different target population. For example, commercial sex workers who are not brothel-based may not face pressure from a manager that would alter their decision-making process.

Case Study 2: Beneficence and Justice

Answer a: Continue the study as designed.

While this is certainly an option, continuing the study may not be in the best interest of the participants. The established high rate of male condom use and the uncertain post-study availability of the female condom make this a poor choice.

Answer b: Terminate the study.

This is the **best answer**. The study may have scientific merit, but this is clearly not the best participant population.

Answer c: Suspend the study. Seek assurance that female condoms will be made reasonably available if proved successful.

This is **not** the best answer. However, it would address the issue of justice. Studying female condoms in a population that will not have access to the product following the study is not a fair distribution of the risks and benefits of the research.

Case Study 3: Informed Consent

Answer a: Recommend that the study be terminated.

This is a drastic option, unless it is clear that the consent process was meaningless and could not be corrected.

Answer b: Retrain the site investigator and the study staff in the informed consent process.

This is the best answer. If documented informed consent is available at the site, and the site is able to recruit and follow the necessary number of study participants, retraining is probably the best option. If the study is to continue, the sponsor and site must be in agreement on how the study procedures and processes are to be conducted.

Answer c: Rely on the site investigator s knowledge of the study population.

This answer, **while not necessarily the best answer**, identifies a choice that happens at many investigative sites. While it may be true that the investigator knows the study population, the approved informed consent form and study procedures were agreed upon **prior** to initiating the study. To change study procedures that are not urgently needed for the safety of the participants (without notifying the sponsor) could affect the entire study. Look for a "better" answer.

Answer d: No action. The site investigator has signed consent forms for each participant.

This is **not** the best answer. Although there is documentation of informed consent in the form of signed documents, this is meaningless and shows a lack of **respect for** persons. Look for a "better" answer.

Case Study 4: Responsibility in Research

Question 1: What guidelines would you give observers for safeguarding client welfare? Is there a point at which intervention is warranted?

The welfare and safety of the client comes first. It should be made clear to study staff from the beginning of their training that they might need to intervene on behalf of a client. Fortunately, such problems will likely be rare, but possible scenarios should be discussed and staff told when and how to react.

Question 2: How should neutral researchers react when they observe mistakes, lapses and misinformation in the context of a study to assess quality of care?

It is the job of the researchers to observe and note such minor mistakes, which are likely to be very common. It is not possible, nor perhaps even desirable, to intervene in every case. "Doing so would prove so intrusive and detrimental to rapport with clinic staff as to ruin the possibility of gathering useful information for program and policy decision-making and thus would greatly lessen the ability to make needed improvements. It is important to discuss fully with relevant local authorities the potential ethical issues that may arise during the implementation of client-provider observations, and the type of behavior by providers that may require some form of intervention by the study observers." [Miller R, et al. *The Situation Analysis Approach to Assessing Family Planning and Reproductive Health Services: A Handbook*. New York: The Population Council, 1997. pp.19-20]

Question 3: Quality of care assessments and performance evaluations are often exempted from the informed consent standards applied to clinical research. What, if any, informed consent procedures should be required of clients? Of providers?

It is essential to provide informed consent to all study participants—providers and clients—even if it is not in writing. "The principle of respect for persons establishes the right of both clients and providers to hear about the nature of the study, about any risks and benefits associated with their participation, and that they can withdraw from the study at any time. Clients must also be informed that they can receive all the services of the health facility whether or not they participate in the study. These issues should be presented in language that is easily understood, and the subject must freely and voluntarily agree to her inclusion in the study. True informed consent also requires that the subject is given the opportunity to ask questions about the study before consenting. It is also important to note that consent should only be obtained when the client is not under duress, in pain, medicated with consciousness-altering drugs, or in need of acute care." [Ibid. p.18.]

Case Study 5: EC Considerations

Answer a: Stop the research to protect the women.

While this is certainly an option, it is an extreme one. It may be worthwhile to look for a way to continue the study and reduce the possibility of violence.

Answer b: Amend the informed consent form and obtain new consent from all participants.

This is a **better answer**. Research often involves some amount of risk, and participants should be aware of the risk before enrolling in a trial. Knowing of this particular risk, some women may decide to not participate.

Answer c: Continue the study, but orally inform participants of the risks.

A **good** answer, but others may be better. Implementing this change would take less time than repeating the written consent process, but the quality of the information may be degraded.

Answer d: Continue the study as designed.

This is **not** the best answer. Ignoring the problem altogether is not in the best interest of the participant. Look at the other answers or a combination of the other answers to address the situation.

Answer e: Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.

This is **not** the best answer. Exposing participants and their partners to retaliation by the plantation managers may cause more violent outbursts. However, it may be advisable to amend the intervention to include information about domestic violence.

Case Study 6: Negative Media Coverage

Question 1: Would you continue your research study?

a. This was the position of some but not all researchers and policy-makers; those rejecting the call to stop research noted that the product had been used for years, had not been shown unsafe in earlier studies, and that the reported study results are preliminary (i.e., could change).

b. This was the position of some but not all researchers; one large study evaluating the product for less deadly infections continued to completion a couple of months after the report, with no harmful effects on participants. A clinical trial with a longer time to completion may have been difficult to complete in light of the negative media coverage.

c. A viable option scientifically, but difficult in light of negative media coverage.

Question 2: Should women who were past or current participants in studies of this product be informed of the data announced at the international conference?

a. This was the decision of one group who had completed a trial; however, others felt that it was more harmful because it could create unnecessary fear about using a marketed product based on incomplete analysis of incomplete data.

b. This was the stance of those who felt it is irresponsible to prematurely release study results, especially when evidence from other studies have not shown the product to be unsafe. How would you adequately explain results released in a 10-minute presentation that did not provide information for judging the quality of the data, had not been peer reviewed, and was based on incomplete data?

Case Study 7: Research with Minors

Question 1: Given the country s conservative culture, should parental permission be sought for this study?

a. While it is important to discuss your research with school officials and make sure they are comfortable with what you are doing, the final decision to waive parental permission must be made by the ethics committee. They may, however, write letters of support to the ethics committee in which they document their policies.

b. Children have to be the age of consent in the study country. This is not a reason to waive parental consent.

c. The local culture must be considered when a research study is being designed. Information gained during pre-study collaboration should be shared with the ethics committee.

d. This answer is not necessarily wrong; however, it should not be the sole determining factor. It is possible that students' answers will be influenced if they think that their parents could possibly have access to the responses. Working closely with school officials and the ethics committees will help guide this process.

Question 2: If it is determined that parental permission is not required, what mechanisms could be incorporated to ensure that students participate voluntarily and to protect them from peer pressure, discrimination by teachers, etc?

a. This is an excellent idea. It would be good to implement this in conjunction with answers 2b and 2c as well.

b. This is a good idea. It would be most useful if parents received a short training session from the researchers on issues related to confidentiality and protection of participants' rights. It would also be good in combination with answers 2a and 2c.

c. This is a good idea as far as it goes, but there is a question of whether the parents actually get the information from the students. It is a good adjunct to answers 2a and 2b.

d. **This is the best answer**. The more community education and feedback in any research, especially with adolescent research, the better.

Case Study 8: Conflict of Interest

Question 1: Do you continue to include this health center in your study?

This is certainly a problematic situation for which there is no perfect answer. The public's perception of this particular clinic—that it provides the best care—must be weighed here. If your research is to benefit the community, then it may be important to use this clinic. Also consider that *not* using this clinic may send the wrong signal to the community, thereby damaging the clinic's excellent standing in the community.

Question 2: Are there effective alternatives to providing condoms to infected participants?

Finding acceptable alternatives may eliminate any lingering doubts about the study's ethical underpinnings. What steps has the clinic taken in the past to prevent infection of partners? Will you be allowed to mention condoms as part of the study even though you cannot provide them? An examination of these questions may lead to an acceptable alternative, and answers will vary.

Question 3: The trial does not depend upon the provision of condoms and could still be conducted. Do you have a moral obligation to the participants?

Answers to this question will vary. While it is true that the research could be conducted without condoms, the researcher's obligation to participants cannot be dismissed. While the research would not necessarily expose participants to *additional* harm, the exposure to any unnecessary risk as a part of research may not be acceptable. Are withholding condoms an unnecessary risk?

Evaluations

Research Ethics Training Curriculum
Pre-test and Post-test Questionnaires

Instructions for Presenters

This pre-test questionnaire should be given before the training session to ascertain knowledge level of the audience. The post-test questionnaire is the same instrument and should be given again after the training to assess how much the audience learned from the presentation.

The following steps are recommended:

- Clarify any terms that may not be familiar to the participants.
- Do not tell the participants that there will be a test again after the presentation (to avoid biasing the results of the post-test).
- Remain in the room during the test.
- Ask the participants to complete the questionnaires individually.
- Check responses against the answer sheet after you have collected all post-tests.

When the questionnaire is used as a "for credit" questionnaire, FHI will be glad to deliver certificates of completion to those participants who complete the post-test questionnaire.

At the end of this section, you will find a *Reader s Evaluation*. Please return completed *Reader s Evaluation* forms and comments to:

Office of International Research Ethics
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
USA

Research Ethics Training Curriculum
Pre-test

Name or Identification Number:_____

Chapter I: Principles of Research Ethics. Circle the correct answer(s).

1. *Which of the following statements define the human research principle of respect for persons?*
   a. The capacity and rights of all individuals to make their own decisions
   b. The respect for the autonomy of all human beings
   c. The recognition of the dignity and freedom of all persons
   d. The need to provide special protection to vulnerable persons
   e. All of the above

2. *Which of the following statements define the human research principle of beneficence?*
   a. Secure the participant's physical, mental and social well-being
   b. Reduce the participant's risks to a minimum
   c. Protection of the participant is more important than the pursuit of new knowledge
   d. Protection of the participant is more important than personal or professional research interest
   e. All of the above

3. *Which of the following statements define the human research principle of justice?*
   a. The selection of participants must be done in an equitable manner
   b. Using research participants for the exclusive benefit of more privileged groups is not permitted
   c. Groups such as minors and pregnant women need special protection
   d. The poor and those with limited access to health care services need special protection
   e. All of the above

Chapter II: Foundations of Research Ethics. Circle the correct answer(s).

4. *According to the* Nuremberg Code*:*
   a. Military doctors should never conduct medical research
   b. The voluntary consent of the human subject is absolutely essential
   c. Research must not be conducted in times of war
   d. Research should be regulated by an international agency
   e. All of the above

5. *The* Declaration of Helsinki *was revised in 2000. This revision prohibits the use of placebos:*
   a. In psychiatric research where a washout period could prove harmful
   b. In less developed countries where participants cannot afford standard therapy
   c. In research with children
   d. In cases where proven prophylactic, diagnostic or therapeutic method exists
   e. All of the above

6. The Belmont Report*, which sets forth the basic ethical principles that govern the conduct of research involving human subjects, was developed in response to:*
   a. Nazi experiments on prisoners in concentration camps
   b. Placebo-controlled AZT studies in Africa
   c. Research conducted on pregnant women
   d. The Tuskegee syphilis study
   e. *The Common Rule*

7. *The Common Rule governs:*
   a. Research funded by the U.S. government
   b. All research on new drugs
   c. All research conducted in the United States
   d. All of the above
   e. None of the above

8. *Published in 1993, the CIOMS guidelines specifically address:*
   a. Conflict of interest
   b. The accreditation of research centers
   c. International research
   d. The use of new designs in research
   e. Behavioral research

9. *The goal of the ICH guidelines is to:*
   a. Globally standardize the drug development and approval process
   b. Regulate ethics committees
   c. Encourage the use of pregnant women and children in research
   d. Set standards for non-biomedical research
   e. None of the above

10. *ALL guidelines for research involving human subjects require:*
    a. Elimination of placebo controls
    b. Benefits for all research participants
    c. Voluntary participation by subjects
    d. Publication of all study findings
    e. Research in animals before research in humans

Chapter III: Responsible Conduct of Research. Circle the correct answer(s).

11. *Which **2** of the following statements are essential elements of the definition of research?*
    a. A systematic investigation
    b. A protocol approved by a scientific review group
    c. A confirmation of recently obtained new knowledge
    d. Develops or contributes to generalizable knowledge
    e. Contributes to the advancement of science

12. *Which **3** of the following statements are essential characteristics of informed consent?*
    a. The participant has received the necessary information
    b. The provision of information has been made in the presence of a witness
    c. The participant has understood the information
    d. The participant arrived at a decision without undue influence or inducement
    e. The information has been presented in a written document

13. The Common Rule *identifies 8 essential elements of informed consent. Which 3 elements are* **not** *included in the following list?*
    Description of the research and expected participation
    Description of risks
    Description of other alternatives to participation
    Explanation of compensation policy for possible injuries
    Explanation that research is voluntary
    a. _____
    b. _____
    c. _____

Indicate true or false.

14.
    a. In a randomized trial, participants should not be informed that they may not be receiving any actual treatment. True ? False ?
    b. The foreseeable risks presented in the informed consent do not require review and approval by an Ethical Review Committee. True ? False ?
    c. Participants do not have to be informed of alternative treatments available. True ? False ?
    d. Participants may not withdraw from the study without prior agreement with the investigator. True ? False ?
    e. Participants who withdraw from the study are not eligible for any type of compensation. True ? False ?

15.

a. Informed consent is mostly a legal requirement, rather than an ethical obligation. True ? False ?
b. Written documentation of informed consent is usually required. True ? False ?
c. The information in informed consent must be presented in a manner that is comprehensible to the potential participant. True ? False ?
d. Informed consent must be obtained by a third party without direct interest in the research. True ? False ?
e. The researcher's special cultural or intellectual status should not play a role in inducing the potential research participant decision. True ? False ?

16.

It is the researcher s responsibility to:

a. Develop scientifically correct research protocols. True ? False ?
b. Ensure that informed consent is appropriately obtained prior to the study initiation. True ? False ?
c. Ensure that the potential participant has understood the information. True ? False ?
d. Obtain Ethics Review Committee approval of any protocol changes. True ? False ?
e. Look out for the best interests of the participants. True ? False ?

17.

A Serious Adverse Event (SAE) is by definition:

a. Related to the study. True ? False ?
b. Only related to physical harm. True ? False ?
c. Unexpected. True ? False ?
d. Something to report to the EC. True ? False ?
e. Requires ending the research. True ? False ?

Chapter IV: Oversight of Research. Circle the correct answer(s).

18. *To be effective, ECs require:*

a. Members who are unaffiliated with the institution
b. Members who are qualified scientists
c. That the institution designates adequate resources
d. All of the above
e. None of the above

19. *It is important that ECs include:*
    a. Members with relevant scientific expertise
    b. Representatives from the community
    c. Members with a diversity of age, gender and cultural background
    d. Both a and b
    e. All of the above

20. *ECs should be notified of:*
    a. Changes to the protocol or consent form
    b. Addition of new research implementation sites
    c. Changes in recruitment procedures
    d. Problems encountered that could impact participant safety
    e. All of the above

21. *When reviewing a study, the EC does NOT consider which of the following:*
    a. Recruitment methods
    b. Informed consent process
    c. Risks to subjects
    d. Publication plans
    e. Confidentiality of research records

22. *In addition to ECs, research may be monitored by:*
    a. _____
    b. _____
    c. _____

Chapter V: Special Issues. Circle the correct answer(s).

23. *What is included in the definition of scientific misconduct:*
    a. Fabrication, falsification, plagiarism or other practices that significantly deviate from accepted standards
    b. Laboratory errors
    c. Differences in interpretation of results
    d. Unexpected results
    e. None of the above

24. *Which of the following is not a potential contributor to conflict of interest:*
    a. The institution
    b. Peer-reviewed journals
    c. Sponsors
    d. The researcher
    e. All of the above

25. *Which 3* ***substantial contributions*** *must be met for authorship?*

a. Funding of the project
b. Conception and design, or analysis and interpretation of data
c. Drafting or critically revising the article for important intellectual content
d. Mentorship of young researchers conducting the study
e. Final approval of the version to be published

Research Ethics Training Curriculum
Post-test

Name or Identification Number:_____

Chapter I: Principles of Research Ethics. Circle the correct answer(s).

1. *Which of the following statements define the human research principle of respect for persons?*
   a. The capacity and rights of all individuals to make their own decisions
   b. The respect for the autonomy of all human beings
   c. The recognition of the dignity and freedom of all persons
   d. The need to provide special protection to vulnerable persons
   e. All of the above

2. *Which of the following statements define the human research principle of beneficence?*
   a. Secure the participant's physical, mental and social well-being
   b. Reduce the participant's risks to a minimum
   c. Protection of the participant is more important than the pursuit of new knowledge
   d. Protection of the participant is more important than personal or professional research interest
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3. *Which of the following statements define the human research principle of justice?*
   a. The selection of participants must be done in an equitable manner
   b. Using research participants for the exclusive benefit of more privileged groups is not permitted
   c. Groups such as minors and pregnant women need special protection
   d. The poor and those with limited access to health care services need special protection
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Chapter II: Foundations of Research Ethics. Circle the correct answers.

4. *According to the* Nuremberg Code*:*
   a. Military doctors should never conduct medical research
   b. The voluntary consent of the human subject is absolutely essential
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Chapter III: Responsible Conduct of Research. Circle the correct answer(s).

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Research Ethics Training Curriculum
Answer Key to Pre-test and Post-test
(Correct answers are bolded.)

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    d. Publication of all study findings
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Chapter III: Responsible Conduct of Research. Circle the correct answer(s).

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    - **d. Develops or contributes to generalizable knowledge**
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    Description risks
    Description of other alternatives to participation
    Explanation of compensation policy for possible injuries
    Explanation that research is voluntary
    - a. **Confidentiality**
    - b. **Benefits**
    - c. **Contact information**

Indicate true or false.

14.
    - a. In a randomized trial, participants should not be informed that they may not be receiving any actual treatment. True ? **False ?**
    - b. The foreseeable risks presented in the informed consent do not require review and approval by an Ethical Review Committee. True ? **False ?**
    - c. Participants do not have to be informed of alternative treatments available. True ? **False ?**
    - d. Participants may not withdraw from the study without prior agreement with the investigator. True ? **False ?**
    - e. Participants who withdraw from the study are not eligible for any type of compensation. True ? **False ?**

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   a. Informed consent is mostly a legal requirement, rather than an ethical obligation. True ? **False ?**
   b. Written documentation of informed consent is usually required. **True ?** False ?
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16. *It is the researcher s responsibility to:*
   a. Develop scientifically correct research protocols. **True ?** False ?
   b. Ensure that informed consent is appropriately obtained prior to the study initiation. **True ?** False ?
   c. Ensure that the potential participant has understood the information. **True ?** False ?
   d. Obtain Ethics Review Committee approval of any protocol changes. **True ?** False ?
   e. Look out for the best interests of the participants. **True ?** False ?

17. *A Serious Adverse Event (SAE) is by definition:*
   a. Related to the study. True ? **False ?**
   b. Only related to physical harm. **True ?** False ?
   c. Unexpected. True ? **False ?**
   d. Something to report to the EC. **True ?** False ?
   e. Requires ending the research. True ? **False ?**

Chapter IV: Oversight of Research. Circle the correct answer(s).

18. To be effective, ECs require:
   a. Members who are unaffiliated with the institution
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    a. Members with relevant scientific expertise
    b. Representatives from the community
    c. Members with a diversity of age, gender and cultural background
    d. Both a and b
    e. All of the above

20. *ECs should be notified of:*
    a. Changes to the protocol or consent form
    b. Addition of new research implementation sites
    c. Changes in recruitment procedures
    d. Problems encountered that could impact participant safety
    e. All of the above

21. *When reviewing a study, the EC does NOT consider which of the following:*
    a. Recruitment methods
    b. Informed consent process
    c. Risks to subjects
    d. Publication plans
    e. Confidentiality of research records

22. *In addition to ECs, research may be monitored by:*
    a. Clinical research organizations
    b. Regulatory agencies
    c. Public interest groups

Chapter V: Special Issues. Circle the correct answer(s).

23. *What is included in the definition of scientific misconduct:*
    a. Fabrication, falsification, plagiarism or other practices that significantly deviate from accepted standards
    b. Laboratory errors
    c. Differences in interpretation of results
    d. Unexpected results
    e. None of the above

24. *Which of the following is not a potential contributor to conflict of interest:*
    a. The institution
    b. Peer-reviewed journals
    c. Sponsors
    d. The researcher
    e. All of the above

*25. Which **3 substantial contributions** must be met for authorship?*

a. Funding of the project
b. Conception and design, or analysis and interpretation of data
c. Drafting or critically revising the article for important intellectual content
d. Mentorship of young researchers conducting the study
e. Final approval of the version to be published

Research Ethics Training Curriculum
Reader s Evaluation

Please answer the questions below after the *Research Ethics Training Curriculum* presentation. The information you provide will help FHI improve future presentations.

Please print and include a business card.

Name	
Address	
Phone	
Fax	
E-mail	
Country(ies) where you work	

What are your current job responsibilities? (Please mark all that apply.)
? Ethics committee member
? Health trainer
? Health care provider
? Medical faculty
? Student (medical, nursing, midwifery, behavioral/medical research)
? Biomedical researcher
? Social science researcher
? Other (specify)_____

Please tell us what you think about the presentation.

Did you take the course: (Please mark one box.)
? Alone ? In a group setting ? On a computer/electronic version
? Using the binder

Did the presentation address what you consider to be the most important research ethical issues? (Please mark one box.) ? Yes No?

What information, if any, should have been covered but was not included? (Please specify)

_____

What part of the presentation, if any, should have been excluded? (Please specify)

_____

How familiar were you with the information in the curriculum prior to this presentation? (Please mark one box.)
? Very familiar ? Somewhat familiar ? Not at all familiar

Which 2 presentation messages do you think will be the most useful to you?
1. _____
2. _____

How did you benefit from attending this presentation? (Please mark all that apply.)
? Learned more about basic research ethics principles

? Learned more about informed consent

? Learned more about ethical review committees

? Improved understanding through the case studies

? Gained a new perspective related to research ethics

? Have increased confidence in working with human subjects

? Did not benefit

? Other (specify)_____

Based on the information presented today, would you consider making any changes to the conduct of research at your institution? ? Yes No?

If Yes, what changes would you consider?

_____

If No, why would you not consider making any changes?

_____

Please respond to each of the following statements by marking the box that best describes your feelings.

The information presented was relevant to my job.
? Strongly agree ? Agree ? Disagree ? Strongly disagree

The slides and other visual aids enhanced my understanding of the presentation content.
? Strongly agree ? Agree ? Disagree ? Strongly disagree

The training activities enhanced my understanding of the presentation content.
? Strongly agree ? Agree ? Disagree ? Strongly disagree

The case studies were relevant to my field of research.
? Strongly agree ? Agree ? Disagree ? Strongly disagree

The duration of the presentation was appropriate.
? Strongly agree ? Agree ? Disagree ? Strongly disagree

Please rate the following presentation components.

	Excellent	Good	Fair	Poor	Non-Applicable
Transparencies					
CD-ROM					
Note pages					
Articles/references					
Pre-test/post-test					
Training activities					
Case studies					
Other (specify)					

Would you recommend the curriculum to colleagues? Why or why not?

_____
_____

Please add any additional comments or suggestions.

_____
_____
_____
_____

Thank you for your assistance.

Please return completed form to:

Office of International Research Ethics
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709
USA

Please send me a certificate of completion.

_____ _____
(Signature) (Date)

Slide Masters

Overview

- Principles of Research Ethics
- Foundations of Research Ethics
- Responsible Conduct of Research
- Supervision of Research
- Special Issues in Research

Principles of Research Ethics

Learning Objectives:

- Learn about the 3 fundamental principles of research ethics
- List and consider vulnerable populations when including human participants in research studies
- Answer questions in 2 case studies

Dale Greer

Fundamental Principles of Human Research Ethics

- **Respect for persons**
- **Beneficence**
- **Justice**

FHI / N. Herndon

Respect for Persons

- **Autonomy, self-determination**
- **Vulnerable persons need special protection**
  - **…**
  - **…**
  - **…**

Respect for Persons (continued)

- Autonomy, self-determination
- Protection of vulnerable groups
  - — those with limited education
  - — the poor
  - — those with difficult access to health services
  - — women
- Informed consent

Case Study 1: Respect for Persons

What steps can the research staff take to ensure that informed consent is freely given by all participants?

If a woman chooses not to participate in the study, what can be done to protect her from retaliation by the manager?

If you believe that the women will not be able to give voluntary informed consent, what alternatives could you suggest to the Ministry of Health?

Beneficence

- **Physical, mental and social well-being**
- **Risks reduced to a minimum**
- **Protection of the participant is the overriding responsibility of the researcher**

FHI / N. Herndon

Justice

- Distribution of risk and benefit
- Equitable recruitment of research participants
- Special protection for vulnerable groups

Case Study 2: Beneficence and Justice

What is the best way to proceed?

a. **Continue the study as designed.**

b. **Terminate the study.**

c. **Suspend the study. Seek assurance that female condoms will be made available if proved successful.**

Foundations of Research Ethics

Learning Objective:

- **Discuss some of the incidents and history that have lead to developing universal research ethics**

Dale Greer

The Evolution of Research Ethics

Codes, guidelines and regulations developed to observe the rules of the road for research involving human participants.

The Nuremberg Code

- **Informed consent is absolutely essential**
- **Qualified researchers use appropriate research designs**
- **Favorable risk/benefit ratio**
- **Participant must be free to stop at any time**

Webshots

The Declaration of Helsinki

- "The well-being of the subject should take precedence over the interests of science and society"
- Consent should be in writing
- Use caution if participant is in dependent relationship with researcher
- Limited use of placebo
- Greater access to benefit

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

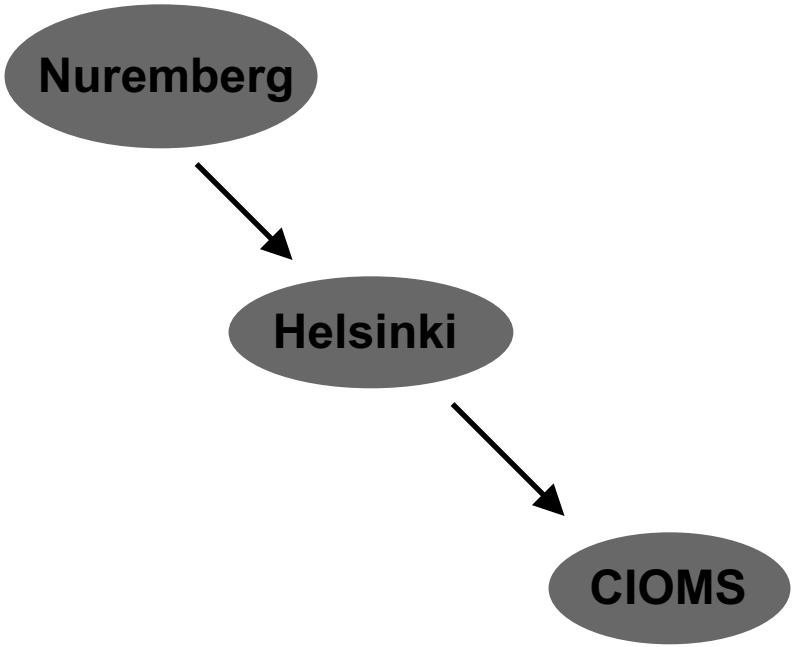
- Respect for persons
- Beneficence
- Justice

FHI / N. Herndon

The U.S. Code of Federal Regulations (also called *The Common Rule*)

- **Prior approval by ethics committee**
- **Written informed consent and documentation**
- **Equitable recruitment of research participants**
- **Special protection for vulnerable groups**
- **Continuing review of approved research**

Council for International Organizations of Medical Science (CIOMS) Guidelines



- informed consent
- research in developing countries
- protection of vulnerable populations
- distribution of the burdens and benefits
- role of ethics committees

International Conference on Harmonization (ICH)

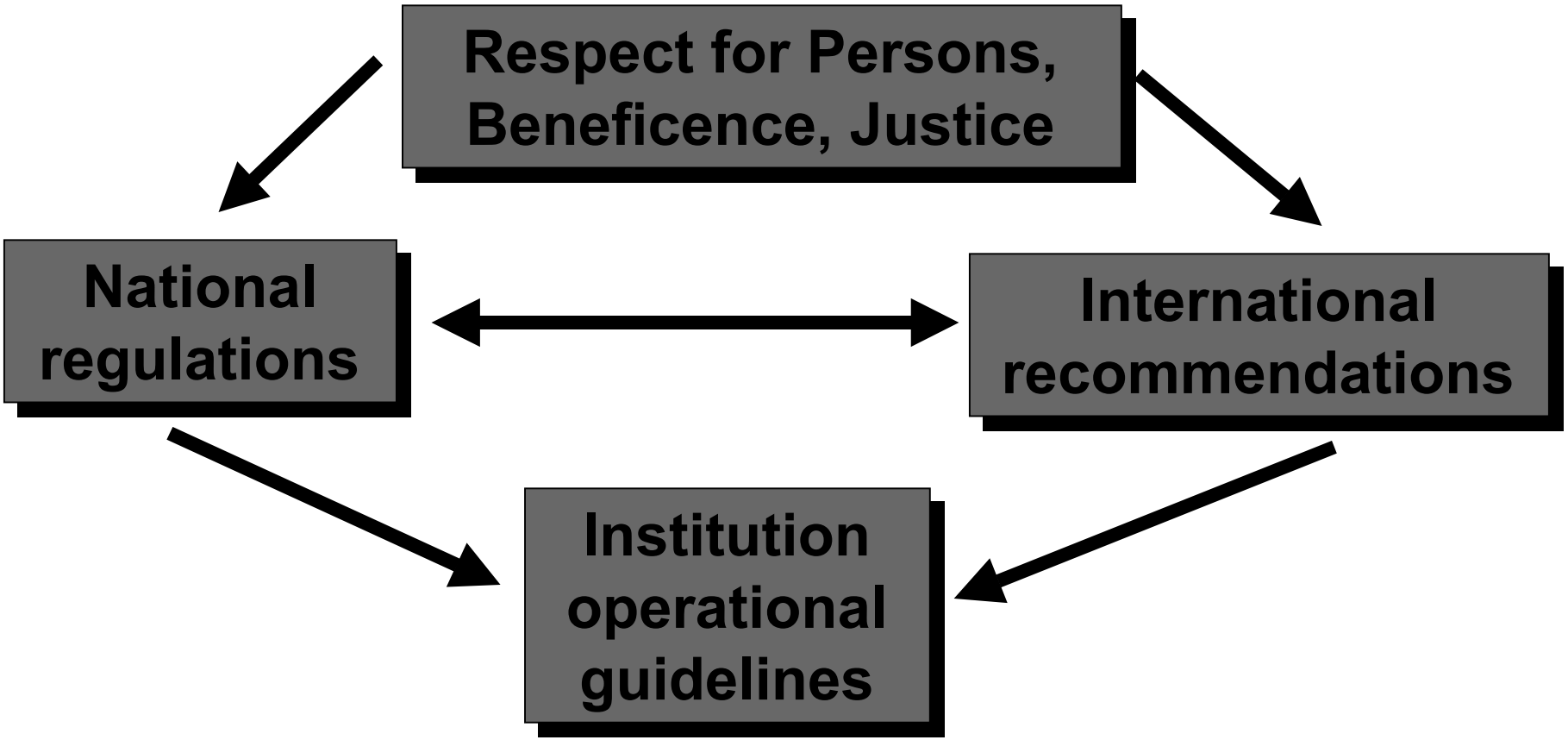
- Standardize drug development and approval process
- Protocol development standards
- Review by ethics committee
- Researcher responsibilities
- Sponsor responsibilities

National Bioethics Advisory Committee (NBAC)

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

- Responsive to local needs
- Community involvement
- Placebo use only when justified
- Access to benefits
- Focus on informed consent

From Fundamental Ethical Principles to Local Guidelines



Local Regulations and Guidelines

- **Many countries now have national guidelines**
- **Rapid growth of research on a global scale**
- **Greatest need is in developing countries**

Summary—Principles and Foundations of Research Ethics

- **All codes and regulations advocate 3 fundamental principles:**
  - **respect for persons**
  - **beneficence**
  - **justice**
- **Research is a privilege, not a right**
- **The well-being of the participant is paramount**

Responsible Conduct of Research

Learning Objectives:

- **Define some key terms**
- **Consider the essential elements of informed consent**
- **Answer questions in 2 case studies**

Dale Greer

What is Research?

Research is:

- **a systematic investigation designed to produce generalizable knowledge**

Research results are usually:

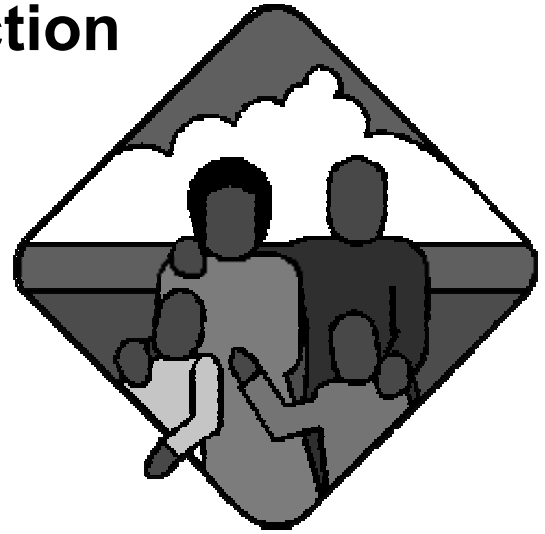
- **applied to other populations**
- **published and disseminated**

Who are Research Participants?

Research participants are

living individuals about whom a researcher conducting research obtains

- **data through intervention or interaction**
- **identifiable private information**



Source: U.S. Code of Federal Regulations

What is Informed Consent?

Informed consent is … "consent given by a competent individual who

- **has received the necessary information**
- **has adequately understood the information**
- **after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation."**

Source: CIOMS International Ethical Guidelines

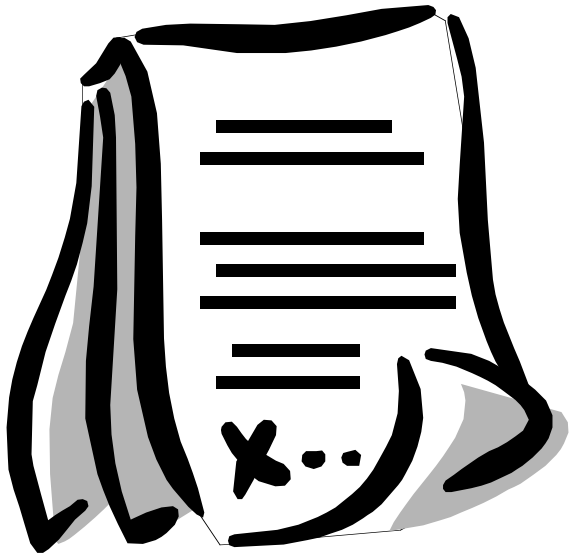
Informed Consent as a Process

Informed consent is a communication process:

- **between the researcher and the participant**
- **starts before the research is initiated**
- **continues throughout the duration of the study**

Essential Elements of Informed Consent

- Research description
- Risks
- Benefits
- Alternatives
- Confidentiality
- Compensation
- Contacts
- Voluntary participation



Description of the Research

- Research study
- Objectives of the study
- Expected responsibilities
- Procedures involved
- Study duration
- Explanation of randomization or placebo

Description of Risks

- **Anticipated or foreseeable**
- **Physical, social, psychological**
- **Culturally appropriate**

FHI / D. Borasky

Description of Benefits

- **Reasonably expected**
- **No exaggeration**
- **Benefits available once research is ended**

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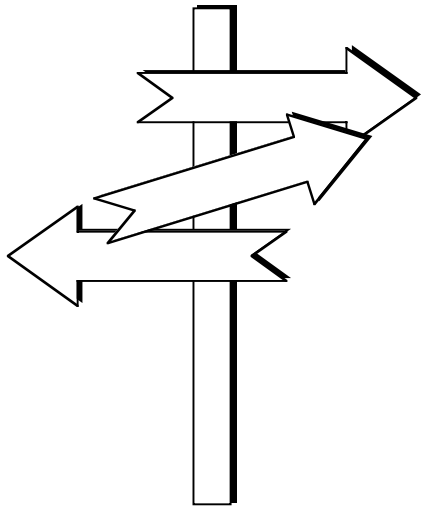
Available Alternatives

- **Alternative procedures or treatment**
- **Advantages and disadvantages**
- **Availability**

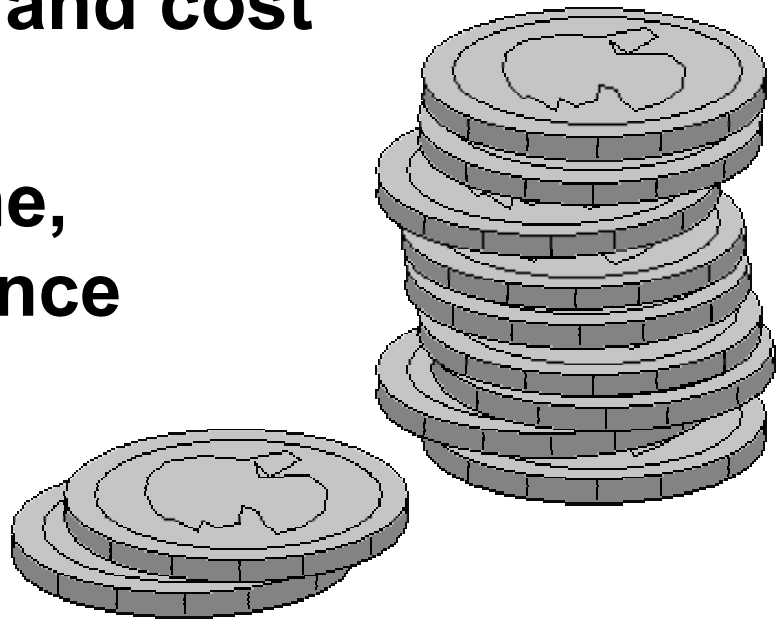


Confidentiality

- **Degree of confidentiality**
- **Indicate persons or organizations who may have access to the information**
- **Special cultural circumstances**

Compensation

- **Available compensation in case of injury**
- **Treatment available and cost**
- **Fair payment for time, travel or inconvenience**
- **Not coercive**



Participant Contacts

- **Contact for research-related questions**
- **Contact for concerns about rights as a participant**
- **Realistic and viable**

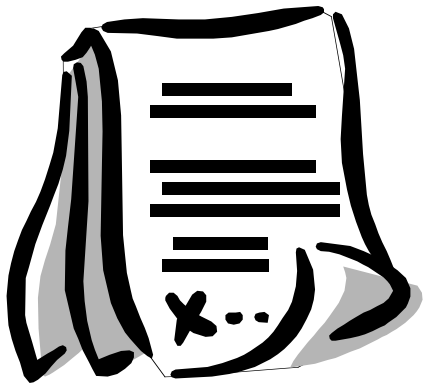
FHI / B. Robinson

Voluntary Participation

- **Absolutely voluntary**
- **Right to discontinue at any time**
- **No penalty for refusal**

Documentation of Informed Consent

- **Part of the informed consent process**
- **May not always be necessary**
- **Ethics Committee review and approval**



Waiver of Informed Consent

- **Minimal risk**
- **Rights and welfare of participants protected**
- **Research not possible without a waiver**
- **Appropriate information provided**

Summary—Informed Consent

- **Moral, not just legal requirement**
- **Comprehensibility essential**
- **Cultural influences**
- **Support information helpful**
- **Possibility for pre-testing**
- **Free of coercion**

Case Study 3: Informed Consent

In this case, the ethics committee should:

a. **Recommend that the study be terminated.**

b. **Retrain the site investigator and the study staff in the informed consent process.**

c. **Rely on the site investigator's knowledge of the study population.**

d. **No action. The site investigator has signed consent forms for each participant.**

Researcher's Responsibilities

Protection of human participants

- **Scientific correctness**
- **Appropriate informed consent**
- **Confidentiality protection**

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Researcher's Responsibilities (continued)

- Conduct research according to protocol
- Compliance with EC requirements
  - — Report adverse experiences, protocol violations, participant complaints
- Post-study
  - — Long-term interests of participants

Researcher's Human Qualities

- Integrity
- Respect
- Compassion
- Professionalism
- Courtesy
- Sensitivity

FHI / R. Kohler

Sponsor's Responsibilities

- **Ensure appropriate review, approval and supervision by an EC**
- **Monitor the research**
- **Select qualified researchers**
- **Provide policies and procedures**

Sponsor's Responsibilities in International Research

- Comply with the local ethical, regulatory and legal requirements
- Ensure the local relevance of the research while involving local partners in the development stages
- Promote research integrity

Summary—Responsible Conduct of Research

Shared responsibilities in research process

- **Well-designed research**
- **Adequately reviewed**
- **Ethically conducted**
- **Properly disseminated**

Case Study 4: Responsibility in Research

What guidelines would you give observers for safeguarding client welfare? Is there a point at which intervention is warranted?

How should neutral researchers react when they observe mistakes, lapses and misinformation in the context of a study to assess quality of care?

Quality of care assessments and performance evaluations are often exempted from the informed consent standards applied to clinical research. What, if any, informed consent procedures should be required of clients? Of providers?

Supervision of Research

Learning Objectives:

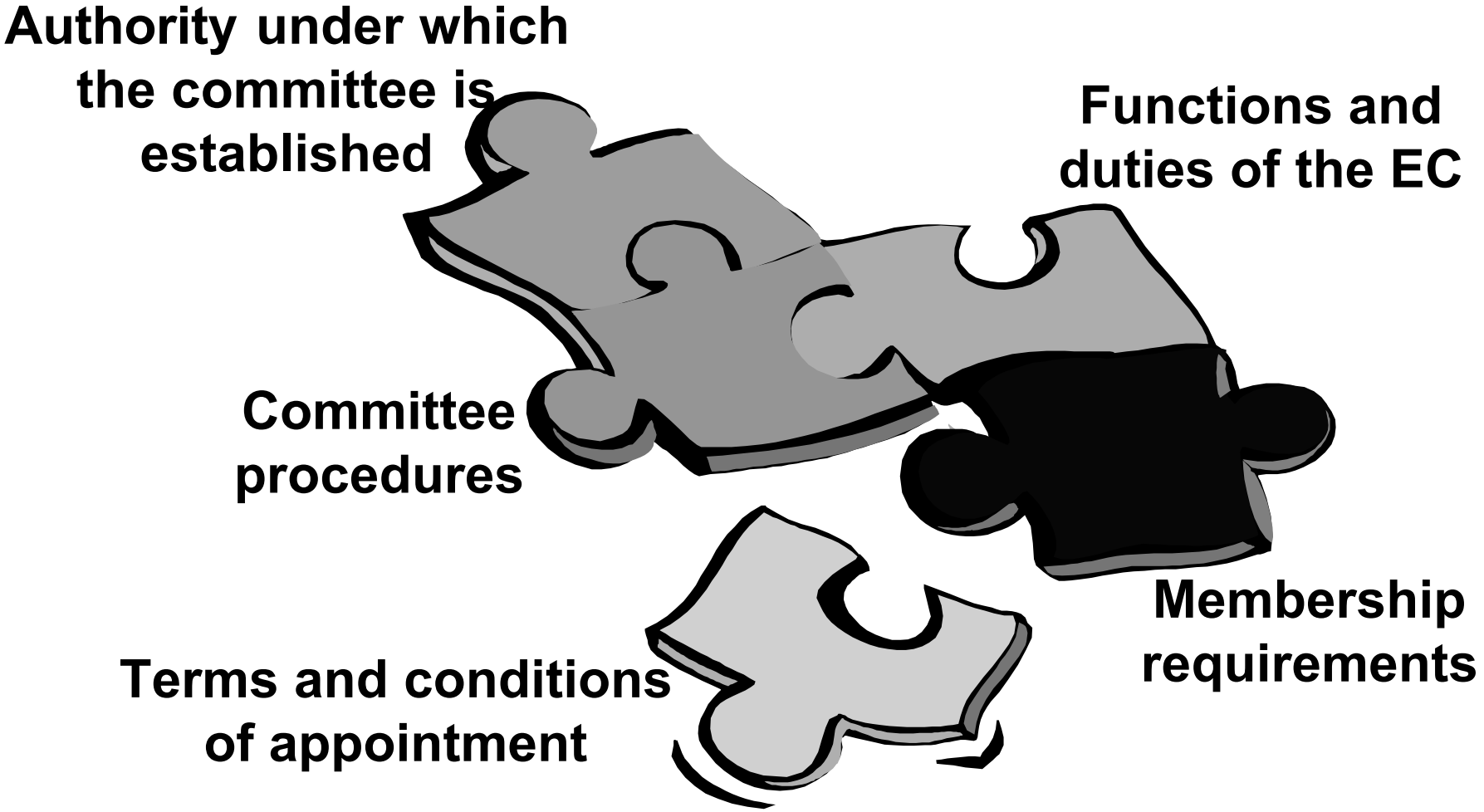
- Describe the role, composition and function of ethical review committees
- Examine adverse event reporting
- Answer questions in a case study

Dale Greer

Research Supervision: Ethics Committees

- Required by ethical guidelines
- Names of committees vary by location
- Primary directive is to protect human research participants

The EC and the Role of the Institution



Ethics Committee Members

Must be qualified to:

- **assess the research**
- **represent the interests of the community where the research will be conducted**

Ethics Committee Membership

Qualified

- Area of expertise aligned with type of research
- Local community representatives
- Clergy or other community leaders
- Former study participants

Diverse

- Sex
- Age
- Cultural Background

Ethics Committees: Criteria for Review and Approval

Scientific Design and Conduct of the Research

- Appropriate research design?
- Qualified researchers?

Recruitment of Research Participants

- Appropriate recruitment methods?
- Safeguards for vulnerable populations?

Community Considerations

- Benefit to community?
- Consultation with community?

Ethics Committees: Criteria for Review and Approval (continued)

Care and Protection of Research Participants

- During and after the research?
- Monitoring of the research?

Informed Consent

- Complete information?
- Written documentation?

Confidentiality Issues

- Adequate protection?
- Risk from breach?

Ethics Committees: Post-approval Role

ECs should be notified of the following:

- …
- …
- …
- …

Ethics Committees: Post-approval Role (continued)

ECs should be notified of the following:

- Changes to the protocol and consent form
- Addition of new research implementation sites
- Changes in recruitment procedures
- Problems encountered that could impact the safety of participants

Monitoring Research: Under the Microscope

Research may be monitored by:

- Sponsor
- ECs
- Regulatory agencies
- Data safety monitoring boards
- Public interest groups

Adverse Event Reporting

- **Serious**
- **Unexpected**
- **Related**

Agencia Fotográfica/ A .Borrero

Summary—Supervision of Research

- ECs are essential to research
- ECs must follow specific guidelines and regulations
- EC review may enhance the research study

Case Study 5: EC Considerations

How should the EC advise the researcher?

a. Stop the research to protect the women.

b. Amend the informed consent form and obtain new consent from all participants.

c. Continue the study, but orally inform participants of the risks.

d. Continue the study as designed.

e. Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.

Special Issues in Research

Learning Objective:

- **Examine conflict of interest and scientific misconduct**

Aztech New Media

Conflict of Interest

The Institution

- bring in research funds
- publish on a regular basis

Research Sponsors

- implement studies
- produce favorable results

The Researcher

- desire private, financial gain
- earn prestige/respect of peers

Preventing Conflict of Interest

- **Prevention is an institutional responsibility**
- **Education and supervision can prevent conflict of interest**
- **Researchers should disclose possible conflicts of interest**

Scientific Misconduct

Scientific misconduct includes willful:

Authorship

Based only on substantial contributions to:

- **Conception and design, or analysis and interpretation of data**
- **Drafting the article or critically revising for important intellectual content**
- **Final approval of the version to be published**

Summary—Special Issues in Research

- **Conflict of interest**
- **Scientific misconduct**
- **Publication of research results**

… are important special issues to consider

Conclusion

- **Additional material in this curriculum**
- **Post-test and certification**
- **For more information contact:**

Office of International Research Ethics
Family Health International
2224 E. NC Highway 54
Durham, NC 27713 USA
E-mail: *ethics@fhi.org*
Web site: *www.fhi.org*

References

Research Ethics Training Curriculum
List of References

Useful Internet Sites for Researchers and Ethics Committee Members

Selected Bibliography

45CFR46

1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS)

Operational Guidelines for Ethics Committees That Review Biomedical Research

World Medical Association Declaration of Helsinki

The Belmont Report

Research Ethics Training Curriculum
Useful Internet Sites for
Researchers and Ethics Committee Members

CDC Associate Director for Science	**http://www.cdc.gov/od/ads/**
CIOMS	**http://www.cioms.ch/index.html**
European Network for Biomedical Ethics	**http://endebit.izew.uni-tuebingen.de/bme/**
MCWIRB IRB/EC Forum (Electronic ERC forum)	**http://www.mcwirb.org**
NIH Bioethics Resources on the Web	**http://www.nih.gov/sigs/bioethics/**
NIH Online Training in Human Subject Protections	**http://cme.nci.nih.gov/**
Program on Ethical Issues in International Health Research at the Harvard School of Public Health	**http://www.hsph.harvard.edu/bioethics/**
The Nuffield Council on Bioethics	**http://www.nuffield.org/bioethics/**
United Nations Universal Declaration of Human Rights	**http://www.un.org/Overview/rights.html**
University of Minnesota Web-Based Instruction on Informed Consent	**http://www.research.umn.edu/consent/orientation.html**
USAID Interpretive Guide to *The Common Rule*	**http://www.usaid.gov/pop_health/resource/phncomrule2.htm**
U.S. FDA Information Sheets	**http://www.fda.gov/oc/oha/IRB/toc.html**
U.S. National Bioethics Advisory Committee	**http://bioethics.gov/**
U.S. Office of Human Research Protections	**http://ohrp.osophs.dhhs.gov/**
U.S. Office of Research Integrity	**http://ori.dhhs.gov/**
World Health Organization	**http://www.who.int/**
World Medical Association	**http://www.wma.net/**

Research Ethics Training Curriculum

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45 CFR 46

Complete document available on line at
<**www4.law.cornell.edu/cfr/45p46.htm**>

This is only Title 45 Part 46,
Public Welfare and the Protection of Human Subjects,
as it pertains to the subject matter.

(c) Absent exceptional cir-cumstances, as determined by the Sec-retary or his or her designee, the De-partment will not entertain a request either to agree to indemnify or to set-tle a personal damage claim before entry of an adverse verdict, judgment or monetary award.
(d) When an employee of the Depart-ment of Health and Human Services be-comes aware that an action has been filed against the employee in his or her individual capacity as a result of con-duct taken within the scope of his or her employment, the employee should immediately notify the Department that such an action is pending.
(e) The employee may, thereafter, re-quest either (1) indemnification to sat-isfy a verdict, judgment or award en-tered against the employee or (2) pay-ment to satisfy the requirements of a settlement proposal. The employee shall submit a written request, with documentation including copies of the verdict, judgment, award or settlement proposal, as appropriate, to the head of his employing component, who shall thereupon submit to the General Coun-sel, in a timely manner, a rec-ommended disposition of the request. The General Counsel shall also seek the views of the Department of Justice. The General Counsel shall forward the request, the employing component's recommendation and the General Counsel's recommendation to the Sec-retary for decision.
(f) Any payment under this section either to indemnify a Department of Health and Human Services employee or to settle a personal damage claim shall be contingent upon the availabil-ity of appropriated funds of the em-ploying component of the Department of Health and Human Services.

AUTHORITY: 5 U.S.C. 301.

[53 FR 11280, Apr. 6, 1988]

PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Sec.

Subpart B—Additional Protections Pertain-ing to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Subpart C—Additional Protections Pertain-ing to Biomedical and Behavioral Re-search Involving Prisoners as Subjects

Subpart D—Additional Protections for Children Involved as Subjects in Research

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289.
EDITORIAL NOTE: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to dem-onstration projects, approved under section 1115 of the Social Security Act, which test the use of cost—sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

AUTHORITY: 5 U.S.C. 301; 42 U.S.C. 289, 42 U.S.C. 300v–1(b).
SOURCE: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§ 46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human sub-jects conducted, supported or otherwise subject to regulation by any federal de-partment or agency which takes appro-priate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such proce-dural modifications as may be appro-priate from an administrative stand-point. It also includes research con-ducted, supported, or otherwise subject to regulation by the federal govern-ment outside the United States.

(1) Research that is conducted or sup-ported by a federal department or agency, whether or not it is regulated as defined in § 46.102(e), must comply with all sections of this policy.

(2) Research that is neither con-ducted nor supported by a federal de-partment or agency but is subject to regulation as defined in § 46.102(e) must be reviewed and approved, in compli-ance with § 46.101, § 46.102, and § 46.107 through § 46.117 of this policy, by an in-stitutional review board (IRB) that op-erates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by de-partment or agency heads, research ac-tivities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational set-tings, involving normal educational practices, such as (i) research on regu-lar and special education instructional strategies, or (ii) research on the effec-tiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of edu-cational tests (cognitive, diagnostic, aptitude, achievement), survey proce-dures, interview procedures or observa-tion of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) any disclosure of the human sub-jects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of edu-cational tests (cognitive, diagnostic, aptitude, achievement), survey proce-dures, interview procedures, or obser-vation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal stat-ute(s) require(s) without exception that the confidentiality of the personally identifiable information will be main-tained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or di-agnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be iden-tified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or sub-ject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise exam-ine:

(i) Public benefit or service pro-grams;

(ii) procedures for obtaining benefits or services under those pro-grams;

(iii) possible changes in or al-ternatives to those programs or proce-dures; or (iv) possible changes in meth-ods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or en-vironmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspec-tion Service of the U.S. Department of Agriculture.

(c) Department or agency heads re-tain final judgment as to whether a particular activity is covered by this

policy.
(d) Department or agency heads may require that specific research activities or classes of research activities con-ducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.
(e) Compliance with this policy re-quires compliance with pertinent fed-eral laws or regulations which provide additional protections for human sub-jects.
(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.
(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which pro-vide additional protections to human subjects of research.
(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the proce-dures prescribed by the institution af-ford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the proce-dural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the de-partment or agency head, notices of these actions as they occur will be pub-lished in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.
(i) Unless otherwise required by law, department or agency heads may waive

[1] Institutions with HHS-approved assur-ances on file will abide by provisions of title 45 CFR part 46 subparts A–D. Some of the other Departments and Agencies have incor-porated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemp-tion at 45 CFR 46.101(b)(2), for research in-volving survey or interview procedures or ob-servation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not par-ticipate in the activities being observed.

the applicability of some or all of the provisions of this policy to specific re-search activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the de-partment or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§ 46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or em-ployee of any department or agency to whom authority has been delegated.
(b) *Institution* means any public or private entity or agency (including fed-eral, state, and other agencies).
(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospec-tive subject to the subject's participa-tion in the procedure(s) involved in the research.
(d) *Research* means a systematic in-vestigation, including research devel-opment, testing and evaluation, de-signed to develop or contribute to gen-eralizable knowledge. Activities which meet this definition constitute re-search for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
(e) *Research subject to regulatio*n, and similar terms are intended to encom-pass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, In-vestigational New Drug requirements administered by the Food and Drug Ad-ministration). It does not include re-search activities which are inciden-tally regulated by a federal department or agency solely as part of the depart-ment's or agency's broader responsibil-ity to regulate certain types of activi-ties whether research or non-research in nature (for example, Wage and Hour requirements administered by the De-partment of Labor).
(f) *Human subject* means a living indi-vidual about whom an investigator (whether professional or student) con-ducting research obtains
(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.
Intervention includes both physical pro-cedures by which data are gathered (for example, venipuncture) and manipula-tions of the subject or the subject's en-vironment that are performed for re-search purposes. Interaction includes communication or interpersonal con-tact between investigator and subject.
Private information includes informa-tion about behavior that occurs in a context in which an individual can rea-sonably expect that no observation or recording is taking place, and informa-tion which has been provided for spe-cific purposes by an individual and which the individual can reasonably expect will not be made public (for ex-ample, a medical record). Private infor-mation must be individually identifi-able (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the in-formation) in order for obtaining the information to constitute research in-volving human subjects.
(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this pol-icy.

(h) *IRB approval* means the deter-mination of the IRB that the research has been reviewed and may be con-ducted at an institution within the constraints set forth by the IRB and by other institutional and federal require-ments.
(i) *Minimal risk* means that the prob-ability and magnitude of harm or dis-comfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of rou-tine physical or psychological exami-nations or tests.
(j) *Certification* means the official no-tification by the institution to the sup-porting department or agency, in ac-cordance with the requirements of this policy, that a research project or activ-ity involving human subjects has been reviewed and approved by an IRB in ac-cordance with an approved assurance.

§ 46.103 Assuring compliance with this policy—research conducted or sup-ported by any Federal Department or Agency.

(a) Each institution engaged in re-search which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of re-quiring submission of an assurance, in-dividual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an as-surance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protec-tion from Research Risks, HHS.
(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB pro-vided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:
(1) A statement of principles govern-ing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regu-lation. This may include an appro-priate existing code, declaration, or statement of ethical principles, or a statement formulated by the institu-tion itself. This requirement does not preempt provisions of this policy appli-cable to department- or agency-sup-ported or regulated research and need not be applicable to any research ex-empted or waived under § 46.101 (b) or (i).
(2) Designation of one or more IRBs established in accordance with the re-quirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping du-ties.
(3) A list of IRB members identified by name; earned degrees; representa-tive capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each mem-ber's chief anticipated contributions to IRB deliberations; and any employ-ment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB member-ship shall be reported to the depart-ment or agency head, unless in accord with § 46.103(a) of this policy, the exist-ence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.
(4) Written procedures which the IRB

will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects re-quire review more often than annually and which projects need verification

from sources other than the investiga-tors that no material changes have oc-curred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a re-search activity, and for ensuring that such changes in approved research, during the period for which IRB ap-proval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appro-priate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or deter-minations of the IRB and (ii) any sus-pension or termination of IRB ap-proval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations im-posed by this policy and shall be filed in such form and manner as the depart-ment or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the de-partment or agency and such experts or consultants engaged for this purpose as the department or agency head de-termines to be appropriate. The depart-ment or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the an-ticipated scope of the institution's re-search activities and the types of sub-ject populations likely to be involved, the appropriateness of the proposed ini-tial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period dur-ing which any particular approved as-surance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal de-partment or agency and not otherwise exempted or waived under § 46.101 (b) or (i). An institution with an approved as-surance shall certify that each applica-tion or proposal for research covered by the assurance and by § 46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or pro-posal or by such later date as may be prescribed by the department or agen-cy to which the application or proposal is submitted. Under no condition shall research covered by § 46.103 of the Pol-icy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. In-stitutions without an approved assur-ance covering the research shall certify within 30 days after receipt of a request for such a certification from the de-partment or agency, that the applica-tion or proposal has been approved by the IRB. If the certification is not sub-mitted within these time limits, the application or proposal may be re-turned to the institution.

(Approved by the Office of Management and Budget under control number 9999–0020)

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991]

§§ 46.104—46.106 [Reserved]

§ 46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly con-ducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as com-munity attitudes, to promote respect for its advice and counsel in safeguard-ing the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the ac-ceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and

practice. The IRB shall therefore in-clude persons knowledgeable in these areas. If an IRB regularly reviews re-search that involves a vulnerable cat-egory of subjects, such as children, prisoners, pregnant women, or handi-capped or mentally disabled persons, consideration shall be given to the in-clusion of one or more individuals who are knowledgeable about and experi-enced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's con-sideration

of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.
(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
(d) Each IRB shall include at least one member who is not otherwise affili-ated with the institution and who is not part of the immediate family of a person who is affiliated with the insti-tution.
(e) No IRB may have a member par-ticipate in the IRB's initial or continu-ing review of any project in which the member has a conflicting interest, ex-cept to provide information requested by the IRB.
(f) An IRB may, in its discretion, in-vite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:
(a) Follow written procedures in the same detail as described in § 46.103(b)(4) and, to the extent required by, § 46.103(b)(5).
(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meet-ings at which a majority of the mem-bers of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a ma-jority of those members present at the meeting.

§ 46.109 IRB review of research.

(a) An IRB shall review and have au-thority to approve, require modifica-tions in (to secure approval), or dis-approve all research activities covered by this policy.
(b) An IRB shall require that infor-mation given to subjects as part of in-formed consent is in accordance with § 46.116. The IRB may require that in-formation, in addition to that specifi-cally mentioned in § 46.116, be given to the subjects when in the IRB's judg-ment the information would meaning-fully add to the protection of the rights and welfare of subjects.
(c) An IRB shall require documenta-tion of informed consent or may waive documentation in accordance with § 46.117.
(d) An IRB shall notify investigators and the institution in writing of its de-cision to approve or disapprove the pro-posed research activity, or of modifica-tions required to secure IRB approval of the research activity. If the IRB de-cides to disapprove a research activity, it shall include in its written notifica-tion a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
(e) An IRB shall conduct continuing review of research covered by this pol-icy at intervals appropriate to the de-gree of risk, but not less than once per year, and shall have authority to ob-serve or have a third party observe the consent process and the research.

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§ 46.110 Expedited review procedures for certain kinds of research involv-ing no more than minimal risk, and for minor changes in approved re-search.

(a) The Secretary, HHS, has estab-lished, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with

other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REG-ISTER. A copy of the list is available from the Office for Protection from Re-search Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.
(b) An IRB may use the expedited re-view procedure to review either or both of the following:
(1) Some or all of the research ap-pearing on the list and found by the re-viewer(s) to involve no more than mini-mal risk,
(2) Minor changes in previously ap-proved research during the period (of one year or less) for which approval is authorized.
Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more ex-perienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the au-thorities of the IRB except that the re-viewers may not disapprove the re-search. A research activity may be dis-approved only after review in accord-ance with the non-expedited procedure set forth in § 46.108(b).
(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of re-search proposals which have been ap-proved under the procedure.
(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institu-tion's or IRB's use of the expedited re-view

procedure.

§ 46.111 Criteria for IRB approval of research.

(a) In order to approve research cov-ered by this policy the IRB shall deter-mine that all of the following require-ments are satisfied:

(1) Risks to subjects are minimized:

(i) By using procedures which are con-sistent with sound research design and which do not unnecessarily expose sub-jects to risk, and (ii) whenever appro-priate, by using procedures already being performed on the subjects for di-agnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distin-guished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research in-volving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economi-cally or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representa-tive, in accordance with, and to the ex-tent required by § 46.116.

(5) Informed consent will be appro-priately documented, in accordance with, and to the extent required by § 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to en-sure the safety of subjects.

(7) When appropriate, there are ade-quate provisions to protect the privacy of subjects and to maintain the con-fidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been in-cluded in the study to protect the rights and welfare of these subjects.

§ 46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review

and approval or disapproval by officials of the institution. However, those offi-cials may not approve the research if it has not been approved by an IRB.

§ 46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to sus-pend or terminate approval of research that is not being conducted in accord-ance with the IRB's requirements or that has been associated with unex-pected serious harm to subjects. Any suspension or termination of approval shall include a statement of the rea-sons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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§ 46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institu-tion. In the conduct of cooperative re-search projects, each institution is re-sponsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoid-ing duplication of effort.

§ 46.115 IRB records.

(a) An institution, or when appro-priate an IRB, shall prepare and main-tain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals re-viewed, scientific evaluations, if any, that accompany the proposals, ap-proved sample consent documents, progress reports submitted by inves-tigators, and reports of injuries to sub-jects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show at-tendance at the meetings; actions taken by the IRB; the vote on these ac-tions including the number of members voting for, against, and abstaining; the basis for requiring changes in or dis-approving research; and a written sum-mary of the discussion of controverted issues and their resolution.

(3) Records of continuing review ac-tivities.

(4) Copies of all correspondence be-tween the IRB and the investigators.

(5) A list of IRB members in the same detail as described is § 46.103(b)(3).

(6) Written procedures for the IRB in

the same detail as described in § 46.103(b)(4) and § 46.103(b)(5).
(7) Statements of significant new findings provided to subjects, as re-quired by § 46.116(b)(5).
(b) The records required by this pol-icy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be acces-sible for inspection and copying by au-thorized representatives of the depart-ment or agency at reasonable times and in a reasonable manner.
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§ 46.116 General requirements for in-formed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the inves-tigator has obtained the legally effec-tive informed consent of the subject or the subject's legally authorized rep-resentative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient oppor-tunity to consider whether or not to participate and that minimize the pos-sibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the sub-ject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the rep-resentative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the insti-tution or its agents from liability for negligence.
(a) Basic elements of informed con-sent. Except as provided in paragraph

(c) or (d) of this section, in seeking in-formed consent the following informa-tion shall be provided to each subject:
(1) A statement that the study in-volves research, an explanation of the purposes of the research and the ex-pected duration of the subject's partici-pation, a description of the procedures to be followed, and identification of any procedures which are experi-mental;
(2) A description of any reasonably foreseeable risks or discomforts to the subject;
(3) A description of any benefits to the subject or to others which may rea-sonably be expected from the research;
(4) A disclosure of appropriate alter-native procedures or courses of treat-ment, if any, that might be advan-tageous to the subject;
(5) A statement describing the ex-tent, if any, to which confidentiality of records identifying the subject will be maintained;
(6) For research involving more than minimal risk, an explanation as to whether any compensation and an ex-planation as to whether any medical treatments are available if injury oc-curs and, if so, what they consist of, or where further information may be ob-tained;
(7) An explanation of whom to con-tact for answers to pertinent questions about the research and research sub-jects' rights, and whom to contact in the event of a research-related injury to the subject; and
(8) 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 par-ticipation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
(b) Additional elements of informed consent. When appropriate, one or more of the following elements of in-formation shall also be provided to each subject:
(1) 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 be-come pregnant) which are currently unforeseeable;
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's con-sent;
(3) Any additional costs to the sub-ject that may result from participation in the research;
(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue par-ticipation will be provided to the sub-ject; and
(6) The approximate number of sub-jects involved in the study.
(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the ele-ments of informed consent set forth above, or waive the requirement to ob-tain informed consent provided the IRB finds and documents that:
(1) The research or demonstration project is to be conducted by or subject to the approval of state or local gov-ernment officials and is designed to study, evaluate, or otherwise examine:
(i) Public benefit of service programs;
(ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to

those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not practica-bly be carried out without the waiver or alteration.
(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the ele-ments of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the subjects;
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) The research could not practica-bly be carried out without the waiver or alteration; and

(4) Whenever appropriate, the sub-jects will be provided with additional pertinent information after participa-tion.
(e) The informed consent require-ments in this policy are not intended to preempt any applicable federal, state, or local laws which require addi-tional information to be disclosed in order for informed consent to be le-gally effective.
(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.
(Approved by the Office of Management and Budget under control number 9999–0020)

§ 46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representa-tive. A copy shall be given to the per-son signing the form.
(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:
(1) A written consent document that embodies the elements of informed consent required by § 46.116. This form may be read to the subject or the sub-ject's legally authorized representa-tive, but in any event, the investigator shall give either the subject or the rep-resentative adequate opportunity to read it before it is signed; or
(2) A short form written consent doc-ument stating that the elements of in-formed consent required by § 46.116 have been presented orally to the sub-ject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the rep-resentative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.
(c) An IRB may waive the require-ment for the investigator to obtain a signed consent form for some or all subjects if it finds either:
(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the sub-ject wants documentation linking the subject with the research, and the sub-ject's wishes will govern; or
(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally re-quired outside of the research context.
In cases in which the documentation requirement is waived, the IRB may re-quire the investigator to provide sub-jects with a written statement regard-ing the research.
(Approved by the Office of Management and Budget under control number 9999–0020)

§ 46.118 Applications and proposals lacking definite plans for involve-ment of human subjects.

Certain types of applications for grants, cooperative agreements, or con-tracts are submitted to departments or agencies with the knowledge that sub-jects may be involved within the period of support, but definite plans would not normally be set forth in the applica-tion or proposal. These include activi-ties such as institutional type grants when selection of specific projects is the institution's responsibility; re-search training grants in which the ac-tivities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior ani-mal studies, or purification of com-pounds. These applications need not be reviewed by an IRB before an award may be made. However, except for re-search exempted or waived under § 46.101 (b) or (i), no human subjects may be involved in any project sup-ported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy,

and certification submitted, by the in-stitution,

to the department or agency.

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later pro-posed to involve human subjects in the research, the research shall first be re-viewed and approved by an IRB, as pro-vided in this policy, a certification sub-mitted, by the institution, to the de-partment or agency, and final approval given to the proposed change by the de-partment or agency.

§ 46.120 Evaluation and disposition of applications and proposals for re-search to be conducted or sup-ported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and pro-posals involving human subjects sub-mitted to the department or agency through such officers and employees of the department or agency and such ex-perts and consultants as the depart-ment or agency head determines to be appropriate. This evaluation will take into consideration the risks to the sub-jects, the adequacy of protection against these risks, the potential bene-fits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ 46.121 [Reserved]

§ 46.122 Use of Federal funds.

Federal funds administered by a de-partment or agency may not be ex-pended for research involving human subjects unless the requirements of this policy have been satisfied.

§ 46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about sup-porting or approving applications or proposals covered by this policy the de-partment or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termi-nation or suspension under paragarph (a) of this section and whether the ap-plicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, mate-rially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§ 46.124 Conditions.

With respect to any research project or any class of research projects the de-partment or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head addi-tional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections Pertaining to Research, Devel-opment, and Related Activi-ties Involving Fetuses, Preg-nant Women, and Human in Vitro Fertilization

SOURCE: 40 FR 33528, Aug. 8, 1975, unless otherwise noted.

§ 46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, develop-ment, and related activities involving:

(1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compli-ance with the procedures set forth herein will in any way render inap-plicable pertinent State or local laws

bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in re-viewing activities to which this sub-part is applicable to assure that they conform to appropriate ethical stand-ards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the De-partment of Health and Human Serv-ices to whom authority has been dele-gated.

(b) *Pregnancy* encompasses the period of time from confirmation of implanta-tion (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or ex-traction of the fetus.

(c) *Fetus* means the product of con-ception from the time of implantation (as evidenced by any of the presump-tive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extrac-tion of the fetus, that it is viable.
(d) *Viable* as it pertains to the fetus means being able, after either sponta-neous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respira-tion. The Secretary may from time to time, taking into account medical ad-vances, publish in the FEDERAL REG-ISTER guidelines to assist in determin-ing whether a fetus is viable for pur-poses of this subpart. If a fetus is via-ble after delivery, it is a premature in-fant.
(e) *Nonviable fetus* means a fetus *ex utero* which, although living, is not via-ble.
(f) *Dead fetus* means a fetus *ex utero* which exhibits neither heartbeat, spon-taneous respiratory activity, sponta-neous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).
(g) *In vitro fertilization* means any fer-tilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.
[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Sec-retary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research sci-entists, physicians, psychologists, soci-ologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health and Human Services.
(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the poli-cies and requirements of this part as to ethical issues, involving activities cov-ered by this subpart, raised by individ-ual applications or proposals. In addi-tion, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and proce-dures.
(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be fund-ed by the Department or any compo-nent thereof until the application or proposal has been reviewed by the Board and the Board has rendered ad-vice as to its acceptability from an eth-ical standpoint.
[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978; 59 FR 28276, June 1, 1994]

§ 46.205 Additional duties of the Insti-tutional Review Boards in connec-tion with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:
(1) Determine that all aspects of the activity meet the requirements of this subpart;
(2) Determine that adequate consid-eration has been given to the manner in which potential subjects will be se-lected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed con-sent process (e.g., through such mecha-nisms, when appropriate, as participa-tion by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and interven-ing as necessary through such steps as visits to the activity site and continu-ing evaluation to determine if any un-anticipated risks have arisen);
(3) Carry out such other responsibil-ities as may be assigned by the Sec-retary.
(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Re-view Board has made the determina-tions required under paragraph (a) of this section and the Secretary has ap-proved these determinations, as pro-vided in § 46.120 of Subpart A of this part.
(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designa-tion of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been estab-lished under Subpart A of this part.
[40 FR 33528, Aug. 8, 1975, as amended at 46 FR 8386, Jan. 26, 1981]

§ 46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken un-less:
(1) Appropriate studies on animals and nonpregnant individuals have been completed;
(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activ-ity.
(3) Individuals engaged in the activ-ity will have no part in: (i) Any deci-sions as to the timing, method, and procedures used to terminate the preg-nancy, and (ii) determining the viabil-ity of the fetus at the termination of the pregnancy; and
(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be in-troduced into the procedure for termi-nating the pregnancy solely in the in-terest of the activity.
(b) No inducements, monetary or oth-erwise, may be offered to terminate pregnancy for purposes of the activity.
[40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

§ 46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be in-volved as a subject in an activity cov-ered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.
(b) An activity permitted under para-graph (a) of this section may be con-ducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the fa-ther's informed consent need not be se-cured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the mini-mum extent necessary to meet such needs, or (2) the risk to the fetus im-posed by the research is minimal and the purpose of the activity is the devel-opment of important biomedical knowledge which cannot be obtained by other means.
(b) An activity permitted under para-graph (a) of this section may be con-ducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the preg-nancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonvia-ble fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is via-ble, a fetus ex utero may not be in-volved as a subject in an activity cov-ered by this subpart unless:
(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the devel-opment of important biomedical knowledge which cannot be obtained by other means, or
(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of via-bility.
(b) No nonviable fetus may be in-volved as a subject in an activity cov-ered by this subpart unless:
(1) Vital functions of the fetus will not be artificially maintained,
(2) Experimental activities which of themselves would terminate the heart-beat or respiration of the fetus will not be employed, and
(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.
(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other sub-parts of this part.
(d) An activity permitted under para-graph (a) or (b) of this section may be conducted only if the mother and fa-ther are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.
[40 FR 33528, Aug. 8, 1975, as amended at 43 FR 1759, Jan. 11, 1978]

§ 46.210 Activities involving the dead fetus, fetal material, or the pla-centa.

Activities involving the dead fetus, mascerated fetal material, or cells, tis-sue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of spe-cific requirements.

Upon the request of an applicant or offeror (with the approval of its Insti-tutional Review Board), the Secretary may modify or waive specific require-ments of this subpart, with the ap-proval of the Ethical Advisory Board after such opportunity for public com-ment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modi-fication or waiver and that such bene-fits cannot be gained except through a modification or waiver. Any such modi-fications or waivers will be published as notices in the FEDERAL REGISTER.

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

SOURCE: 43 FR 53655, Nov. l6, l978, unless otherwise noted.

§ 46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and be-havioral research conducted or sup-ported by the Department of Health and Human Services involving pris-oners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compli-ance with the procedures set forth herein will authorize research involv-ing prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarcer-ation which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protec-tion of prisoners involved in activities to which this subpart is applicable.

§ 46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the De-partment of Health and Human Serv-ices to whom authority has been dele-gated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual in-voluntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending ar-raignment, trial, or sentencing.

(d) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medi-cal, dental, or psychological examina-tion of healthy persons.

§ 46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the require-ments in § 46.107 of this part, an Insti-tutional Review Board, carrying out responsibilities under this part with re-spect to research covered by this sub-part, shall also meet the following spe-cific requirements:

(a) A majority of the Board (exclu-sive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner rep-resentative with appropriate back-ground and experience to serve in that capacity, except that where a particu-lar research project is reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8386, Jan. 26, 1981]

§ 46.305 Additional duties of the Insti-tutional Review Boards where pris-oners are involved.

(a) In addition to all other respon-sibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review rep-resents one of the categories of re-search permissible under § 46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her par-ticipation in the research, when com-pared to the general living conditions, medical care, quality of food, amen-ities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is im-paired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner vol-unteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbi-trary intervention by prison authori-ties or prisoners. Unless the principal

investigator provides to the Board jus-tification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that par-ticular research project;
(5) The information is presented in language which is understandable to the subject population;
(6) Adequate assurance exists that parole boards will not take into ac-count a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly in-formed in advance that participation in the research will have no effect on his or her parole; and
(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sen-tences, and for informing participants of this fact.
(b) The Board shall carry out such other duties as may be assigned by the Secretary.
(c) The institution shall certify to the Secretary, in such form and man-ner as the Secretary may require, that the duties of the Board under this sec-tion have been fulfilled.

§ 46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:
(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the re-search under § 46.305 of this subpart; and
(2) In the judgment of the Secretary the proposed research involves solely the following:
(i) Study of the possible causes, ef-fects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than mini-mal risk and no more than inconven-ience to the subjects;
(ii) Study of prisons as institutional structures or of prisoners as incarcer-ated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
(iii) Research on conditions particu-larly affecting prisoners as a class (for example, vaccine trials and other re-search on hepatitis which is much more prevalent in prisons than else-where; and research on social and psy-chological problems such as alcohol-ism, drug addiction and sexual as-saults) provided that the study may proceed only after the Secretary has consulted with appropriate experts in-cluding experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to ap-prove such research; or
(iv) Research on practices, both inno-vative and accepted, which have the in-tent and reasonable probability of im-proving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols ap-proved by the IRB to control groups which may not benefit from the re-search, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REG-ISTER, of his intent to approve such re-search.
(b) Except as provided in paragraph (a) of this section, biomedical or behav-ioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D—Additional Protections for Children Involved as Sub-jects in Research

SOURCE: 48 FR 9818, Mar. 8, 1983, unless oth-erwise noted.

§ 46.401 To what do these regulations apply?

(a) This subpart applies to all re-search involving children as subjects, conducted or supported by the Depart-ment of Health and Human Services.
(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such non-substantive, procedural modifications

as may be appropriate from an admin-istrative standpoint.
(2) It also includes research con-ducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of § 46.101 of Sub-part A, waive the applicability of some or all of the requirements of these reg-ulations for research of this type.
(b) Exemptions at § 46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at § 46.101(b)(2) regarding educational tests is also applicable to this subpart. How-ever, the exemption at § 46.101(b)(2) for research involving survey or interview procedures or observations of public be-havior does not apply to research cov-ered by this subpart, except for re-search involving observation of public behavior when the investigator(s) do not participate in the activities being

observed.
(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of § 46.101 of Subpart A are applicable to this sub-part.
[48 FR 9818, Mar. 8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991]

§ 46.402 Definitions.

The definitions in § 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this sub-part:
(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the re-search will be conducted.
(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, ab-sent affirmative agreement, be con-strued as assent.
(c) *Permission* means the agreement of parent(s) or guardian to the participa-tion of their child or ward in research.
(d) *Parent* means a child's biological or adoptive parent.
(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§ 46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all ap-plicable sections of this subpart.

§ 46.404 Research not involving great-er than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is pre-sented, only if the IRB finds that ade-quate provisions are made for solicit-ing the assent of the children and the permission of their parents or guard-ians, as set forth in § 46.408.

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a mon-itoring procedure that is likely to con-tribute to the subject's well-being, only if the IRB finds that:
(a) The risk is justified by the antici-pated benefit to the subjects;
(b) The relation of the anticipated benefit to the risk is at least as favor-able to the subjects as that presented by available alternative approaches; and
(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual sub-jects, but likely to yield generaliz-able knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being

of the subject, only if the IRB finds that:
(a) The risk represents a minor in-crease over minimal risk;
(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or ex-pected medical, dental, psychological, social, or educational situations;
(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condi-tion which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guard-ians, as set forth in § 46.408.

§ 46.407 Research not otherwise ap-provable which presents an oppor-tunity to understand, prevent, or al-leviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:
(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem af-fecting the health or welfare of chil-dren; and
(b) The Secretary, after consultation with a panel of experts in pertinent dis-ciplines (for example: science, medi-cine, education, ethics, law) and fol-lowing opportunity for public review and comment, has determined either:
(1) That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or
(2) The following:
(i) The research presents a reasonable opportunity to further the understand-ing, prevention, or alleviation of a seri-ous problem affecting the health or welfare of children;
(ii) The research will be conducted in

accordance with sound ethical prin-ciples;
(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for as-sent by children.

(a) In addition to the determinations required under other applicable sec-tions of this subpart, the IRB shall de-termine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of provid-ing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be in-volved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB deter-mines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure in-volved in the research holds out a pros-pect of direct benefit that is important to the health or well-being of the chil-dren and is available only in the con-text of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the sub-jects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sec-tions of this subpart, the IRB shall de-termine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate pro-visions are made for soliciting the per-mission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is suffi-cient for research to be conducted under § 46.404 or § 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from par-ents, both parents must give their per-mission unless one parent is deceased, unknown, incompetent, or not reason-ably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in § 46.116 of Subpart A, if the IRB determines that a re-search protocol is designed for condi-tions or for a subject population for which parental or guardian permission is not a reasonable requirement to pro-tect the subjects (for example, ne-glected or abused children), it may waive the consent requirements in Sub-part A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not incon-sistent with Federal, state or local law. The choice of an appropriate mecha-nism would depend upon the nature and purpose of the activities described in the protocol, the risk and antici-pated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guard-ians shall be documented in accordance with and to the extent required by § 46.117 of Subpart A.

(e) When the IRB determines that as-sent is required, it shall also determine whether and how assent must be docu-mented.

§ 46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under § 46.406 or § 46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hos-pitals, institutions, or similar settings in which the majority of children in-volved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advo-cate for each child who is a ward, in ad-dition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the re-search and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian or-ganization.

PART 50—U.S. EXCHANGE VISITOR PROGRAM—REQUEST FOR WAIV-ER OF THE TWO-YEAR FOREIGN RESIDENCE REQUIREMENT

Sec.

AUTHORITY: 75 Stat. 527 (22 U.S.C. 2451 et seq.); 84 Stat. 116 (8 U.S.C. 1182(e)).

SOURCE: 49 FR 9900, Mar. 16, 1984, unless otherwise noted.

§ 50.1 Authority.

Under the authority of Mutual Edu-cational and Cultural Exchange Act of 1961 (75 Stat. 527) and the Immigration and Nationality Act as amended (84 Stat. 116), the Department of Health and Human Services is an ''interested United States Government agency'' with the authority to request the Unit-ed States Information Agency to rec-ommend to the Attorney General waiv-er of the two-year foreign residence re-quirement for exchange visitors under the Mutual Educational and Cultural Exchange Program.

§ 50.2 Exchange Visitor Waiver Review Board.

(a) *Establishment.* The Exchange Visi-tor Waiver Review Board is established to carry out the Department's respon-sibilities under the Exchange Visitor Program.

(b) *Functions.* The Exchange Visitor Waiver Review Board is responsible for making thorough and equitable evalua-tions of applications submitted by in-stitutions, acting on behalf of exchange visitors, to the Department of HHS for a favorable recommendation to the United States Information Agency that the two-year foreign residence require-ment for exchange visitors under the Exchanges Visitor Program be waived.

(c) *Membership.* The Exchange Visitor Waiver Review Board consists of no

1993 INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in Collaboration with the World Health Organization (WHO)

(Introductory sections, as well as Annexes, Appendices and Acknowledgments are omitted here)

Informed Consent of Subjects

Guideline 1: Individual informed consent

For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative.

Commentary on Guideline 1

General considerations. Informed consent is consent given by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy.

In itself, informed consent is an imperfect safeguard for the individual, and it must always be complemented by independent ethical review of research proposals. Moreover, many individuals, including young children, many adults with severe mental or behavioural disorders, and many persons who are totally unfamiliar with modern medical concepts, are limited in their capacity to give adequate informed consent. Because their consent could imply passive and uncomprehending participation, investigators must on no account presume that consent given by such vulnerable individuals is valid, without the prior approval of an independent ethical-review body. When an individual is incapable of making an informed decision whether to participate in research, the investigator must obtain the proxy consent of the individual's legal guardian or other duly authorized representative.

When the research design involves no more than minimal risk - that is, risk that is no

more likely and not greater than that attached to routine medical or psychological examination - and it is not practicable to obtain informed consent from each subject (for example, where the research involves only excerpting data from subjects' records) the ethical review committee may waive some or all of the elements of informed consent. Investigators should never initiate research involving -human subjects without obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee.

Guideline 2: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding:

- **that each individual is invited to participate as a subject in research, and the aims and methods of the research;**
- **the expected duration of the subject's participation;**
- **the benefits that might reasonably be expected to result to the subject or to others as an outcome of the research;**
- **any foreseeable risks or discomfort to the subject, associated with participation in the research;**
- **any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested;**
- **the extent to which confidentiality of records in which the subject is identified will be maintained;**
- **the extent of the investigator's responsibility, if any, to provide medical services to the subject;**
- **that therapy will be provided free of charge for specified types of research-related injury;**
- **whether the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury; and**
- **that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled.**

Commentary on Guideline 2

Process. Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the subjects, by repetition and explanation, by answering subjects' questions as they arise, and by assuring that each procedure is understood by each subject, the research team not only elicits the informed consent of subjects but also manifests deep respect for the dignity of the subjects.

Language. Informing the subject must not be simply a ritual recitation of the contents of a form. Rather, the investigator must convey the information in words that suit the individual's level of understanding. The investigator must bear in mind that ability to

understand the information necessary to give informed consent depends on the individual's maturity, intelligence, education and rationality.

Comprehension. The investigator must then ensure that the prospective subject has adequately understood the information. This obligation is the more serious as risk to the subject increases. In some instances the investigator might administer an oral or a written test to check whether the information has been adequately understood.

Benefits. In research designed to evaluate vaccines, drugs or other products, subjects should be told whether and how the product will be made available to them if it proves to be safe and effective. They should be told whether they will have continuing access to the product between the end of their participation in the research and the time of approval of the product for general distribution, and whether they will receive it free of charge or will be expected to pay for it.

Risks. In the case of complex research projects it may be neither feasible nor desirable to inform prospective subjects fully about every possible risk. However, they must be informed of all risks that a reasonable person would consider material to making a decision about whether to participate. An investigator's judgment about what risks are to be considered material should be reviewed and approved by the ethical review committee (see Guideline 3). Subjects who desire additional information should be afforded an opportunity to ask questions.

The investigator's responsibility for medical care. If the investigator is a physician, the subject must be told clearly whether the investigator will act only as an investigator or as both an investigator and a physician to the subject. However, an investigator who agrees to act as physician investigator undertakes all of the legal and ethical responsibilities of the subject's primary-care physician. In such a case, if the subject withdraws from the research owing to complications related to the research or in the exercise of the right to withdraw without loss of benefit, the physician has an obligation to continue to provide medical care to the subject, or to see that the subject receives the necessary care in the community or district health-care system, or to offer assistance in finding another physician.

If the investigator is to act only as an investigator, the subject must be advised to seek any necessary medical care, outside the context of the
research.

Other considerations. For further details of the obligation to provide economic compensation in the event of death or disability resulting from specified types of research-related injury, see Guideline 13. For further discussion of confidentiality, see Guideline 12.

Guideline 3: Obligations of ***investigators regarding informed consent***

The investigator has a duty to:

- **communicate to the prospective subject all the information necessary for adequately informed consent;**
- **give the prospective subject full opportunity and encouragement to ask questions;**
- **exclude the possibility of unjustified deception, undue influence and intimidation;**
- **seek consent only after the prospective subject has adequate knowledge of the relevant facts and of the consequences of participation, and has had sufficient opportunity to consider whether to participate;**
- **as a general rule, obtain from each prospective subject a signed form as evidence of informed consent; and**
- **renew the informed consent of each subject if there are material changes in the conditions or procedures of the research.**

Commentary on Guideline 3

Necessary information. The standards for communicating information as set forth in Guidelines 2 and 3 should be regarded as minimum. Other types of information that should be conveyed include the reasons for selecting prospective subjects (ordinarily because they either have certain diseases or have no apparent disease) and certain features of the research design (for example, randomization, double-blind, case control), stated in language that the subjects can understand. Additional types of information that should be conveyed in some circumstances are suggested below in the commentaries on several other guidelines. In general the standard for communicating information is that any and all information that a reasonable person would consider material to reaching a decision about whether to consent should be communicated. Investigators and ethical review committees should determine together what should be communicated in connection with particular studies.

Opportunity to ask questions. The investigator must be prepared to answer all of the subject's questions relating to the proposed research. Any restriction of the subject's ability to ask questions and receive answers before or during the research undermines the validity of the informed consent.

Deception. Sometimes, to ensure valid research, subjects are deliberately misled. In biomedical research, deception mostly takes the form of withholding information about the purpose of procedures; for example, subjects in clinical trials are often not told the purpose of tests performed to monitor their compliance with the protocol, in case that if they knew their compliance was being monitored they would modify their behaviour and thus invalidate the results. In most such cases the prospective subjects are asked to consent to remain uninformed of the purpose of some procedures until the research is completed; in other cases, because a request for permission to withhold some information would jeopardize the validity of the research, prospective subjects are not made aware that some information has been withheld until the research is completed.

Telling lies to subjects is a tactic not commonly employed in biomedical research.

However, social and behavioural scientists may deliberately misinform subjects to study their attitudes and behaviour; for example, scientists have pretended to be patients to study the behaviour of health-care professionals and patients in their natural settings.

Deception of the subject is not permissible in research projects that carry more than minimal risk of harm to the subject. When deception is indispensable to the methods of an experiment, the investigator must demonstrate to an ethical review committee that no other research method would suffice; that significant advances could result from the research; and that nothing has been withheld that, if divulged, would cause a reasonable person to refuse to participate. The ethical review committee with the investigator should determine whether and how deceived subjects should be informed of the deception upon completion of the research. Such informing, commonly called "debriefing", ordinarily entails explaining the reasons for the deception. A subject who disapproves of having been deceived is ordinarily offered an opportunity to refuse to allow the investigator to use information obtained from studying the subject.

Undue influence. The investigator should seek to exclude any undue influence on the subject. However, the borderline between justifiable persuasion and undue influence is imprecise. The investigator should not give the prospective subject any unjustifiable assurances about the benefits, risks or inconveniences of the research. An example of undue influence would be to induce a close relative or a community leader to influence a prospective subject's decision or to threaten to withhold health services. See also Guideline 4.

Intimidation. Intimidation in any form invalidates informed consent. Prospective subjects who are patients often depend upon the investigator for medical care, and the investigator has a certain credibility in their eyes. If the research protocol has a therapeutic component, the investigator's influence over them may be considerable. They may fear, for example, that refusal to participate would damage their relationship with the investigator. The investigator must assure prospective subjects that their decision on whether to participate will not affect the therapeutic relationship or any other benefits to which they are entitled.

Documentation of consent. Consent may be indicated in a number of ways. The subject may imply consent by his or her voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so. The ethical review committee may approve the waiving of the requirement of a signed consent form if the research carries no more than minimal risk and if the procedures to be used are only those for which signed consent forms are not customarily required outside the research context. Such waivers may also be approved when existence of a signed consent form would be an unjustified threat to the subjects' confidentiality. In some cases, particularly when the information is complicated, it is advisable to give subjects information sheets to retain; these may resemble consent forms in all respects except that subjects are not required to sign them.

Continuing consent. The initial consent should be renewed when material changes occur in the conditions or the procedures of the research. For example, new information may have come to light, either from the study or from outside the study, about the risks or benefits of therapies being tested or about alternatives to the therapies. Subjects should be given such information. In many clinical trials, data are not disclosed to subjects and investigators until the study is concluded. This is ethically acceptable if the data are monitored by a committee responsible for data and safety monitoring (see Guideline 14, page 40) and an ethical review committee has approved their non-disclosure.

Guideline 4: Inducement to participate

Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All **payments, reimbursements and medical services to he provided to research subjects should be approved by an ethical review committee.**

Commentary on Guideline 4

Acceptable recompense. Research subjects may have their transport and other expenses reimbursed and receive a modest allowance for inconvenience due to their participation in the research. Also, investigators may provide them with medical services and the use of facilities, and perform procedures and tests free of charge, provided these are done in connection with the research.

Unacceptable recompense. Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may be unduly influenced to participate in research simply to receive such care. Therefore, monetary and in-kind recompense must be evaluated in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence. The ethical review committee will ordinarily be the best judge of what constitutes reasonable material recompense in particular circumstances.

Incompetent persons. Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give proxy consent on behalf of an incompetent person should be offered no remuneration except a refund of out-of-pocket expenses.

Withdrawal from study. When a subject withdraws from research for reasons related to the study, or is withdrawn on health grounds, the investigator should pay the subject as if

full participation had taken place. When a subject withdraws for any other reason, the investigator should pay in proportion to the amount of participation. An investigator who must remove a subject from the study for wilful noncompliance is entitled to withhold part or all of the payment.

Guideline 5: Research involving children

Before undertaking research involving children, the investigator must ensure that:

- **children will not be involved in research that might equally well be carried out with adults;**
- **the purpose of the research is to obtain knowledge relevant to the health needs of children;**
- **a parent or legal guardian of each child has given proxy consent;**
- **the consent of each child has been obtained to the extent of the child's capabilities;**
- **the child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically acceptable alternative;**
- **the risk presented by interventions not intended to benefit the individual child-subject is low and commensurate with the importance of the knowledge to be gained; and**
- **interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child-subject as any available alternative.**

Commentary on Guideline 5

Justification of the involvement of children. The participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible. The aims of the research should be relevant to the health needs of children.

Consent of the child. The willing cooperation of the child should be sought, after the child has been informed to the extent that the child's maturity and intelligence permit. The age at which a child becomes legally competent to give consent differs substantially from one jurisdiction to another; in some countries the "age of consent" established in their different provinces, states or other political subdivisions varies considerably. Often children who have not yet reached the legally established age of consent can understand the implications of informed consent and go through the necessary procedures; they can therefore knowingly agree to serve as research subjects. Such knowing agreement is insufficient to permit participation in research unless it is supplemented by the proxy consent of a parent, legal guardian or other duly authorized representative.

Older children who are capable of informed consent should be selected before younger children or infants, unless there are important scientific reasons related to age for involving younger children first. An objection by a child to taking part in research should always be respected even if the parent gives proxy consent, unless according to the

research protocol the child would receive therapy for which there is no medically acceptable alternative; in such a case parents or guardians may properly be authorized to override the objections of the child, particularly if the child is very young or immature.

Proxy consent of a parent or guardian. The investigator must obtain the proxy consent of the parent or guardian in accordance with local laws or established procedures. It may be assumed that children over the age of 13 years are usually capable of giving informed consent, but their consent must be complemented by the proxy consent of a parent or guardian, unless this is not required by local law.

Observation of research by parent. A parent or guardian who gives proxy consent for a child to participate in research should be given the opportunity to observe the research as it proceeds, so as to be able to withdraw the child from the research if the parent or guardian decides it is in the child's best interests to do so.

Psychological and medical support. Research involving children should be conducted in settings in which the child and the parent can obtain adequate medical and psychological support. As an additional protection for children, an investigator may, when possible, obtain the advice of a child's family physician or other health-care provider on matters concerning the child's involvement in the research.

Justification of risks. Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child-subject must be justified by the expectation that they will be at least as advantageous to the individual child-subject, considering both risks and benefits, as any available alternative. Risks are to be justified in relation to anticipated benefits to the child.

The risk of interventions that are not intended to be of direct benefit to the child-subject must be justified in relation to anticipated benefits to society (generalizable knowledge). In general, the risk from such interventions should be minimal - that is, no more likely and not greater than the risk attached to routine medical or psychological examination of such children. When an ethical review committee is persuaded that the object of the research is sufficiently important, slight increases above minimal risk may be permitted.

Guideline 6. Research involving persons with mental or behavioural disorders

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- **such persons will not be subjects of research that might equally well be carried out on persons in full possession of their mental faculties;**
- **the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;**
- **the consent of each subject has been obtained to the extent of that subject's capabilities, and a prospective subject's refusal to participate in non-clinical research is always respected;**

- **in the case of incompetent subjects, informed consent is obtained from the legal guardian or other duly authorized person;**
- **the degree of risk attached to interventions that are not intended to benefit the individual subject is low and commensurate with the importance of the knowledge to be gained; and**
- **interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual subject as any alternative.**

Commentary on Guideline 6

General considerations. Although the two populations differ in many respects, the ethical considerations discussed earlier in the case of children apply by and large to persons who are unable to give adequately informed consent by reason of mental or behavioural disorders. They should never be subjects of research that might equally well be carried out on adults in full possession of their mental faculties, but they are clearly the only subjects suitable for a large part of research into the origins and treatment of certain severe mental or behavioural disorders.

Consent of the individual. People with mental or behavioural disorders may not be capable of giving adequately informed consent. The willing cooperation of such prospective subjects should be sought to the extent that their mental state permits, and any objection on their part to taking part in any non-clinical research should always be respected. When an investigational intervention is intended to be of therapeutic benefit to a subject, the subject's objection should be respected unless there is no reasonable medical alternative and local law permits overriding the objection.

Proxy consent of the guardian. The Declaration of Helsinki states "In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent... permission from the responsible relative replaces that of the subject in accordance with national legislation" (Article 1. 1 1).
The agreement of an immediate family member - whether spouse, parent, adult offspring or sibling - should be sought, but is sometimes of doubtful value, especially as families sometimes regard persons with mental or behavioural disorders as an unwelcome burden. In the case of an individual who has been committed to an institution by a court order, it may be necessary to seek legal authorization for involving the person in research.

Serious illness in persons who are unable to give adequately informed consent because of mental or behavioural disorders. Such persons who have, or are at risk of, serious illnesses such as HIV infection, cancer or hepatitis should not be deprived of the possible benefits of investigational drugs, vaccines or devices that show promise of therapeutic or preventive benefit, particularly when no superior or equivalent therapy or prevention is available. Their entitlement to access to such therapy or prevention is justified ethically on the same grounds as is such entitlement for other vulnerable groups (see Guideline 10). Persons who are unable to give adequately informed consent by reason of mental or behavioural disorders are, in general, not suitable subjects for formal clinical trials except

those designed to be responsive to their particular health needs. Direct HIV infection of the brain may result in mental impairment; in the case of patients with such impairment, formal clinical trials of drugs, vaccines and other interventions designed to treat or prevent the impairment may be approved by an ethical review committee.

Anticipated incapacity to give informed consent. When it can be reasonably predicted that a competent person will lose the capacity to make valid decisions about medical care, as in the case of early manifestations of cognitive impairment due to HIV infection or Alzheimer's disease, such a person may be asked to designate the conditions, if any, in which he or she would consent to becoming a research subject while unable to communicate, and to designate a person who will consent on his or her behalf in accordance with the subject's previously expressed wishes.

Guideline 7. ***Research involving prisoners***

Prisoners with serious illness or at risk of serious illness should not arbitrarily be denied access to investigational drugs, vaccines or other agents that show promise of therapeutic or preventive benefit.

Commentary on Guideline 7

General considerations. Guideline 7 is not intended as an endorsement of involving prisoners as research subjects. The involvement of volunteer prisoners in biomedical research is permitted in very few countries, and even in those is controversial. Advocates of allowing prisoners to participate in research argue that they are particularly suitable in that they are living in a standard physical and psychological environment; that unlike fully-employed or mobile populations they have time to participate in long-term experiments; and that they regard such participation as relief from the tedium of prison life, evidence of their social worth, and a chance to earn a small income.

Opponents claim that the consent of prisoners cannot be valid in that it is influenced by the hope of rewards and other expectations, such as earlier parole.

Although none of the international declarations bars prisoners from serving as subjects of biomedical research, the contradictory though persuasive arguments preclude an internationally agreed recommendation. However, where the practice is permitted, there should be provision for the independent monitoring of the research projects.

Prisoners and serious illness. Prisoners suffering from or at risk of serious illnesses such as HIV infection, cancer or hepatitis should not be deprived of the possible benefits of investigational drugs, vaccines or devices, particularly when no superior or equivalent products are available. Their entitlement to access to such therapy and prevention is justified ethically on the same grounds as is that of other vulnerable groups (see Guideline 1 0). However, as no diseases afflict prisoners only, one cannot sustain arguments analogous to those supporting the suitability of children and of persons with

mental or behavioural disorders as subjects in formal clinical trials.

Guideline 8: Research involving subjects in underdeveloped communities

Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that:

- **persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities;**
- **the research is responsive to the health needs and the priorities of the community in which it is to be carried out;**
- **every effort will be made to secure the ethical imperative that the consent of individual subjects be informed ; and**
- **the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community.**

Commentary on Guideline 8

General considerations. Diseases that rarely or never occur in economically developed countries or communities exact a heavy toll of illness, disability or death in some communities that are socially and economically at risk of being exploited for research purposes. Research into the prevention and treatment of such diseases is needed and, in general, must be carried out in large part in the countries and communities at risk.

The ethical implications of research involving human subjects are identical in principle wherever the work is undertaken; they relate to respect for the dignity of each individual subject as well as to respect for communities, and protection of the rights and welfare of human subjects. Assessment of inherent risks is a pre-eminent concern. However, a number of subsidiary considerations apply particularly to research undertaken in underdeveloped communities of either developing or developed countries, by investigators and sponsors from developed countries or from developed institutions of developing countries.

Individuals and families in such communities are liable to exploitation for various reasons. Some of them may be relatively incapable of informed consent because they are illiterate, unfamiliar with the concepts of medicine held by the investigators, or living in communities in which the procedures typical of informed-consent discussions are unfamiliar or alien to the ethos of the community. Certain investigators may wish to take advantage of the lack in most developing countries of well-developed regulations or ethical review committees, which could have the effect of delaying access to research subjects; others may find it less expensive to conduct in developing countries research designed to develop drugs and other products for the markets of developed countries.

Guideline 8 is written on the presumption that research in developing countries or

underdeveloped communities will generally be conducted by investigators and sponsored by agencies from developed countries or from developed communities of developing countries. Such investigators or sponsors may encounter practices that would be considered immoral in their own countries. This should be anticipated and the range of acceptable responses by the sponsors and investigators should be detailed in the protocol submitted to an ethical committee for review and approval.

Investigators must respect the ethical standards of their own countries and the cultural expectations of the societies in which research is undertaken, unless this implies a violation of a transcending moral rule. Investigators risk harming their reputation by pursuing work that host countries find acceptable but their own countries find offensive. Similarly, they may transgress the cultural values of the host countries by uncritically conforming to the expectations of their own.

Nature of the research. To guard against exploitation of individuals and families in socially and economically exploitable communities, sponsors and investigators who wish to conduct in such communities research that could be carried out reasonably well in developed communities must satisfy their national or local ethical review committees, and in the case of externally sponsored research the appropriate ethical review committee in the host country, that the research would not be exploitative. The reason for choosing an underdeveloped community should be made explicit.

The research conducted in underdeveloped communities should be responsive to the health needs and priorities of those communities. It should not exhaust resources which the community usually devotes to the health care of its members. If any product is to be developed, such as a new therapeutic agent, clear understanding should be reached among investigators, sponsors, representatives of the collaborating countries, and community leaders about what the community is to expect and what can or cannot be provided during and at the close of the research. Such understanding must be reached before the research is begun, to ensure that the research is truly responsive to the priorities of the community.

As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun.

Phase 1 drug studies and Phase 1 and 11 vaccine studies (Annex 2) should be conducted only in developed communities of the country of the sponsor. In general, Phase 111 vaccine trials and Phase 11 and 111 drug trials should be conducted simultaneously in the host community and the sponsoring country; they may be omitted in the sponsoring country on condition only that the drug or vaccine is designed to treat or prevent a disease or other condition that rarely or never occurs in the sponsoring country.

Informed consent. All reasonable efforts should be made to obtain the informed consent

of each prospective subject according to the standards specified in Guidelines 1 to 3, to ensure that the rights of prospective subjects are respected. For example, when because of communication difficulties investigators cannot make prospective subjects sufficiently aware of the implications of participation to give adequately informed consent, the decision of each prospective subject on whether to consent should be elicited through a reliable intermediary such as a trusted community leader. In some cases other mechanisms, approved by an ethical review committee, may be more suitable. However consent is obtained, all prospective subjects must be clearly told that their participation is entirely voluntary, and that they are free to refuse to participate or to withdraw their participation at any time without loss of any entitlement. The investigator is required to ensure that each prospective subject is clearly told everything that would be conveyed if the study were to be conducted in a developed community and, further, to ensure that earnest attempts are made to enable the prospective subject to understand this information; otherwise, assurance of freedom to refuse or withdraw from participation would be meaningless.

All plans to use the above standard for informing, providing assistance with understanding, and assuring freedom to refuse or withdraw must be approved by an ethical review committee and supplemented with other means of assuring that the rights of prospective subjects are respected.

Ethical review. The ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee must have as either members or consultants persons with such understanding, so that the committee may evaluate proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects. Such persons should be able, for example, to identify appropriate members of the community to serve as intermediaries between investigators and subjects, to decide whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange traditions, and to provide safeguards for data and personal information that subjects consider to be private or sensitive.

HIVIAIDS considerations. HIV infection and AIDS are endemic in many of the world's countries and communities, both developed and developing. Some features of HIV/AIDS justify the involvement of people from underdeveloped communities in epidemiological research relevant to the HIV/AIDS pandemic as well as in research designed to test candidate drugs and vaccines for the treatment and prevention of HIV infection and AIDS. These include, but are not limited to, evidence that modes of transmission of the infection, and the natural history of the disease, may differ substantially among communities. Moreover, strains of HIV are different in various regions of the world, and the current scientific understanding is that different strains may respond differently to vaccines or drugs. If research were conducted only in developed countries and communities, developing countries could be deprived of many of the benefits of such research. Therefore, participation in HIV/AIDS research of inhabitants of appropriately selected underdeveloped communities should be encouraged, provided their rights and welfare are adequately safeguarded as set forth in Guideline 8.

Guideline 9: Informed consent in epidemiological studies

For several types of epidemiological research individual informed consent is either impracticable or inadvisable. In such cases the ethical review committee should determine whether it is ethically acceptable to proceed without individual informed consent and whether the investigator's plans to protect the safety and respect the privacy of research subjects and to maintain the confidentiality of the data are adequate.

Commentary on Guideline 9

General considerations. For epidemiological studies it is normal for investigators to secure the agreement and cooperation of the national or local authority responsible for public health in the population to be studied. In the case of a community in which collective decision-making is customary it is also advisable to seek the agreement of the community, usually through its chosen representatives.

Informed consent. Epidemiological studies that require the examination of documents, such as medical records, or of anonymous "leftover" samples of blood, urine, saliva or tissue specimens may be conducted without the consent of the individuals concerned, as long as their right to confidentiality is assured by the study methods.

When the focus of a study is an entire community rather than individual human subjects - for example, to test the use of an additive in a community's water supply, or a new health care procedure or method, or a new method of control of disease vectors such as mosquitoes or rats - individual consent or an individual's refusal to be exposed to the intervention would be meaningless unless the individual were willing to leave the community. However, individuals may refuse to submit to such procedures as questionnaires or blood tests designed to obtain data for evaluating the intervention.

When epidemiological studies entail personal contact between investigators and individual subjects, the general requirements for informed consent are directly applicable. When they involve individuals primarily as members of population groups, it may be acceptable not to obtain the informed consent of each individual. In the case of population groups with social structures, common customs, and an acknowledged leadership, the investigator will need to secure the cooperation and obtain the agreement of the group's leadership. In the case of groups defined solely in demographic or statistical terms, with neither leaders nor representatives, the investigator must satisfy an ethical review committee that the safety of the research subjects and the confidentiality of the data will be strictly safeguarded.

Consent is not required for the use of publicly available information, but the investigator should know that countries and communities differ with regard to what information about individuals is considered public. Investigators who use such information should avoid disclosure of personally sensitive information.

In the case of studies of certain forms of social behaviour, an ethical review committee may determine that it would be inadvisable to seek individual informed consent because to do so would frustrate the purpose of a study; for example, prospective subjects on being informed of the behaviour to be studied would change the behaviour. The review committee must be satisfied that there will be adequate safeguards of confidentiality and that the importance of the objectives of the research is in proportion to the risks to the subjects.

Investigators who propose to carry out epidemiological studies should consult *International Guidelines for Ethical Review of Epidemiological Studies* (CIOMS, 199 1).

Selection of Research Subjects

Guideline 10: Equitable distribution of burdens and benefits

Individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied.

Commentary on Guideline 10

General considerations. In general, the equitable distribution of the burdens and the benefits of participation in research raises no serious problems when the intended subjects do not include vulnerable individuals or communities. Occasionally, when research is designed to evaluate therapeutic agents widely perceived to offer substantial advantages over those generally available, it may be appropriate to publicize widely the opportunity to participate in the research or to establish outreach programmes for individuals or groups who have no ready access to information about research programmes.

Equitable distribution of the burdens and benefits of research participation is generally more difficult when the intended subjects include vulnerable individuals or groups. Classes of individuals traditionally considered vulnerable are those with limited capacity or freedom to consent. They are the subject of specific guidelines in this publication and include children, persons who because of mental or behavioural disorders are incapable of giving informed consent, and prisoners. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that:

- the research could not be carried out reasonably well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of or unique to the vulnerable class, either the actual subjects or other similarly situated members of the vulnerable class;

- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;
- the risks attached to research that is not intended to benefit individual subjects will be minimal, unless an ethical review committee authorizes a slight increase above minimal risk (see Guideline 5); and
- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the proxy consent of their legal guardians or other duly authorized representatives.

Other vulnerable social groups. The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced by the expectation, whether justified or not, of preferential treatment or by fear of disapproval or retaliation if they refuse. Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police.

Because they work in close proximity to investigators or disciplinary superiors, they tend to be called upon more often than others to serve as research subjects, and this could result in inequitable distribution of the burdens and benefits of research.

Other groups or classes may also be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people and the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless persons, nomads, refugees, and patients with incurable disease. To the extent that these and other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be considered.

Persons with HIV infection or at risk of contracting HIV infection. Persons in this category are not vulnerable in the sense of having limited capacity to consent. However, certain features of HIV infection and of the AIDS pandemic have prompted reconsideration of some aspects of the ethics of research involving human subjects; as a result, various countries have developed policies and practices designed to be responsive to the special problems presented by HIV infection; some of these problems are discussed in the following paragraphs. Although this commentary concerns problems associated with HIV infection, the basic principles apply equally to problems associated with other more or less similar conditions.

Drugs and other therapies that have not yet been licensed for general availability because studies designed to establish their safety and efficacy remain to be completed are sometimes made available to persons with HIV infection. This is compatible with the Declaration of Helsinki, Article 11.1, which states "...the physician must be free to use a new diagnostic or therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering."

Drugs and other therapies that are made available, because they show promise of therapeutic benefit, to persons not considered vulnerable should be made equally available to members of vulnerable populations, particularly when no superior or equivalent approaches to therapy are available; children, pregnant or nursing women, persons with mental disorders who are not capable of giving informed consent, and prisoners are entitled to equal access to the benefits of such investigational agents unless there is good reason, such as a medical contraindication, not to afford such access.

When women take investigational drugs for HIV infection, special precautions are often needed. Women who are not pregnant when they begin to take such drugs should be counselled about reliable contraception. In developed countries, nursing mothers who ask to be treated with investigational drugs for HIV infection should be advised that they must discontinue breast-feeding while taking such drugs, unless there is clear evidence that the drug does not appear in milk. In each case in which an investigational drug is administered to a pregnant or nursing woman, there should be careful monitoring and reporting of the effects, if any, on the fetus or child.

Although it is generally required that research be conducted on less vulnerable populations before involving more vulnerable populations, some exceptions are justified. In general, children are not suitable subjects for Phase 1 drug trials or for Phase I or 11 vaccine trials, but in some cases such trials may be permissible after clinical trials in adults have shown some degree of therapeutic effect. For example, a Phase 11 vaccine trial seeking evidence of immunogenicity in infants may be justified in the case of a vaccine that has shown evidence of preventing or slowing progression from asymptomatic HIV infection to disease in adults. Additional examples are provided in the commentaries on Guidelines 6 and 8.

The life-threatening and infectious nature of HIV/AIDS does not justify any suspension of the rights of research subjects to informed consent, voluntary participation in or withdrawal from the study, or protection of confidentiality. In the case of research protocols that provide for diagnostic tests for HIV infection, the procedures for obtaining informed consent should be supplemented by counselling in which each subject is informed about AIDS and HIV infection, advised to avoid risky behaviour, and advised of the risk of social discrimination against individuals who are thought to be HIV-infected or at risk of such infection. In the case of patients with HIV disease or persons becoming aware of being HIV-infected, research teams should provide them with necessary services or refer them for follow-up.

Participation in drug and vaccine trials in the field of HIV infection and AIDS may impose on the research subjects significant associated risks of social discrimination or harm; such risks merit consideration equal to that given to the adverse medical consequences of the drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, participants in vaccine trials must be enabled to demonstrate that their HIV seropositivity is due to their having been vaccinated rather than to natural infection. This may be accomplished by providing subjects with documents attesting to

their participation in vaccine trials, or by maintaining a confidential register of trial participants, from which information can be made available to outside agencies at a participant's request.

Guideline I]: Selection of pregnant or nursing (breastfeeding) women as research subjects

Pregnant or nursing women should in no circumstances be the subjects of non-clinical research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about pregnancy or lactation. As a general rule, pregnant or nursing women should not be subjects of any clinical trials except such trials as are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

Commentary on Guideline 11

General considerations. In general, pregnant and nursing women are not suitable subjects of formal clinical trials other than those designed to respond to the health needs of such women or their fetuses or nursing infants. Examples of such trials would be a trial designed to test the safety and efficacy of a drug for reducing perinatal transmission of HIV infection from mother to child, a trial of a device for detecting fetal abnormalities, or trials of therapies for conditions associated with or aggravated by pregnancy, such as nausea and vomiting, hypertension or diabetes. The justification for their participation in such clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigational drugs, vaccines or other agents that promise therapeutic or preventive benefit. In all cases risks to women subjects, fetuses and infants should be minimized, as far as sound research design permits.

A woman may decide to discontinue nursing to become eligible to participate in clinical research, but this is not to be encouraged, particularly in developing countries, where cessation of breast-feeding may be harmful to the nursing child and also increase the risk of another pregnancy.

Selection of women as research subjects. Women in most societies have been discriminated against with regard to their involvement in research. Women who are biologically capable of becoming pregnant have been customarily excluded from formal clinical trials of drugs, vaccines, and devices owing to concern about undetermined risks to the fetus. Consequently, relatively little is known about the safety and efficacy of most drugs, vaccines, or devices for such women, and this lack of knowledge can be dangerous. For example, thalidomide caused much more extensive damage than it would have if its first administration to such women had been in the context of a formal, carefully-monitored clinical trial.

A general policy of excluding from such clinical trials women biologically capable of becoming pregnant is unjust in that it deprives women as a class of persons of the

benefits of the new knowledge derived from the trials. Further, it is an affront to their right of self-determination. The exclusion of such women can be justified only on such grounds as evidence or suspicion that a particular drug or vaccine is mutagenic or teratogenic. Nevertheless, although women of childbearing age should be given the opportunity to participate in research, they should be helped to understand that the research could include risks to the fetus.

Premenopausal women have also been excluded from participation in many research activities, including non-clinical studies, that do not entail administration of drugs or vaccines, in case the physiological changes associated with various phases of the menstrual cycle would complicate interpretation of research data. Consequently, much less is known of women's than of men's normal physiological processes. This, too, is unjust in that it deprives women as a class of persons of the benefits of such knowledge.

Informed consent. Obtaining the informed consent of women, including those who are pregnant or nursing, usually presents no special problems. In some cultures, however, women's rights to exercise self-determination and thus give valid informed consent are not acknowledged. In such cases, women should not normally be involved in research for which societies that recognize these rights require informed consent. Nevertheless, women who have serious illnesses or who are at risk of developing such illnesses should not be deprived of opportunities to receive investigational therapies when there are no better alternatives, even though they may not consent for themselves. Efforts must be made to let such women know of these opportunities and to invite them to decide whether they wish to accept the investigational therapy, even though the formal consent must be obtained from another person, usually a man. Such invitations may best be extended by women who understand the culture sufficiently well to discern whether prospective recipients of investigational therapies genuinely wish to accept or reject the therapy.

Research related to termination of pregnancy. No recommendation is made regarding the acceptability of research relating to the termination of pregnancy, or undertaken in anticipation of termination of pregnancy. The acceptability of such research depends on religious belief, cultural traditions and national legislation.

Confidentiality of Data

Guideline 12: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigators' ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality.

Commentary on Guideline 12

General considerations. The Declaration of Helsinki, Article 1.6, states: "The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the

impact of the study on the subject's physical and mental integrity and on the personality of the subject." The customary approach to showing respect for privacy is by obtaining prior informed consent to releases of research data and minimizing the possibility of a breach of confidentiality. If the requirement of individual informed consent is to be waived by an ethical review committee, alternative measures should be taken. Such measures are discussed in *International Guidelines for Ethical Review of Epidemiological Studies* (CIOMS, 1991).

Confidentiality between physician and patient. Patients in therapeutic relationships with their physicians have the right to expect that all information will be held in strict confidence and disclosed only to those who need, or have a legal right to, the information, such as nurses and technicians, to treat the patients. A treating physician should not disclose any identifying data about patients to an investigator unless the patients have first given their consent to such disclosure.

Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiologists and other investigators often make use of such records. In studies of medical records it is usually impracticable to obtain the informed consent of each identifiable patient. Accordingly, an ethical review committee may waive the requirement for informed consent. In institutions in which records may be used for research purposes without the informed consent of identifiable patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement in patient-information brochures.

In the case of research limited to subjects' medical records, access must be approved by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

Confidentiality between investigator and subject. Research relating to individuals and groups may involve the collection and storage of data that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the data, or other means.

Prospective subjects should be informed of limits to the investigators' ability to ensure strict confidentiality and of the foreseeable adverse social consequences of limitations or breaches of confidentiality. In some cases investigators are required to communicate data from records to a national drug registration authority or to an industrial sponsor of the research. Some jurisdictions require the reporting of, for instance, certain communicable diseases to public health authorities or evidence of child abuse or neglect to appropriate agencies. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects.

Compensation of Research Subjects for Accidental Injury

Guideline 13*: Right of subjects to compensation*

Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependants are entitled to material compensation. The right to compensation may not be waived.

Commentary on Guideline 13

Accidental injury. Accidental injury due to procedures performed exclusively to accomplish the purposes of research rarely results in death or in permanent or temporary impairment or disability. Death, impairment or disability is much more likely to result from investigational diagnostic, preventive or therapeutic interventions. In general, however, death or serious injury is less likely to result from investigational therapies administered in the context of properly designed, conducted and sanctioned studies than from similar standard therapies in routine medical practice. Usually, human research subjects are in exceptionally favourable circumstances in that they are under close and continuing observation by qualified investigators alert to detecting the earliest signs of untoward reactions. Such favourable conditions are less likely in medical practice.

Equitable compensation. Compensation is owed to subjects who sustain significant physical injury from procedures performed solely to accomplish the purposes of research. Justice requires that every subject of biomedical research be automatically entitled to fair compensation for any such injury. Compensation is generally not owed to research subjects who suffer expected or foreseen adverse reactions from investigational therapies or other procedures performed to diagnose or prevent disease. Such reactions are not different in kind from those that occur in medical practice.

When, as in the early stages of drug testing, it is unclear whether a procedure is performed primarily for research or for therapeutic purposes, the ethical review committee should determine in advance the injuries for which subjects will be compensated and those for which they will not; prospective subjects should be informed of the review committee's decisions, as part of the informed consent process.

Subjects should not be required to waive their rights to compensation or to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim compensation. The informed consent process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their legal rights, including the right to seek compensation for injury.

In some societies the right to compensation for accidental injury is not acknowledged. Therefore, when giving their informed consent to participate, research subjects should be told whether there is provision for compensation in case of physical injury, and the circumstances in which they or their dependants would receive it.

Obligation of the sponsor to pay. The sponsor, whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any physical injury for which subjects are entitled to compensation. Sponsors are advised to obtain adequate insurance against risks to cover compensation, independent of proof of fault.

Review Procedures

Guideline 14: Constitution and responsibilities of ethical review committees

All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees. The investigator must obtain such approval of the proposal to conduct research before the research is begun.

Commentary on Guideline 14

General considerations. The provisions for review of research involving human subjects are influenced by political institutions, the organization of medical practice and research, and the degree of autonomy accorded to medical investigators. Whatever the circumstances, however, society has a dual responsibility to ensure that:
- all drugs, devices and vaccines under investigation in human subjects meet adequate standards of safety; and
- the provisions of the Declaration of Helsinki are applied in all biomedical research involving human subjects.

Assessment of safety. Authority to assess the safety and quality of medicines and vaccines intended for use in humans is most effectively vested in a multidisciplinary advisory committee. In many cases such committees will function best if they operate at the national level; in other instances they are most effective at regional or local level. Clinicians, clinical pharmacologists, pharmacologists, microbiologists, epidemiologists, statisticians and other experts have important contributions to offer to such assessment. Many countries lack the resources to assess technical data independently according to procedures and standards now required in the more developed countries. Improvement in this respect depends, in the short term, on more efficient exchange of information internationally.

Ethical review committees. Scientific review and ethical review cannot be clearly separated: scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risk or inconvenience to no purpose. Normally, therefore, ethical review committees consider both the scientific and the ethical aspects of proposed research.

Scientific review. The Declaration of Helsinki, Article 1.1, states that "biomedical research involving human subjects must conform to generally accepted scientific

principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature."

Committees competent to review and approve scientific aspects of clinical trials must be multidisciplinary, much like those specified earlier for assessment of safety. In many cases such committees operate most effectively at the national level. A national scientific review committee offers several advantages over local committees. First, consolidating the necessary expertise in one group allows members to deepen their knowledge in the field**,** thereby improving the quality and utility of the review. Second, a national committee's awareness of all proposals for research in the country facilitates the performance of another essential function, the selection of those protocols most likely to achieve the nation's health research objectives.

If an ethical review committee considers a research proposal scientifically sound, or verifies that a competent expert body has found it so, it will then consider whether any known or possible risks to the subjects are justified by the expected benefits (and whether the methods of carrying out the research will minimize harm and maximize benefit) and, if so, whether the procedures proposed for obtaining informed consent are satisfactory and those proposed for selection of subjects are equitable.

Risks and benefits. The Declaration of Helsinki forbids the imposition of unwarranted risks on human research subjects. Article 1.4 requires that "the importance of the objective is in proportion to the inherent risk to the subject." The need for means of preventing or treating HIV infection or AIDS, for example, is obvious justification of research aimed at developing such treatment or prevention. However, it may not be possible to justify clinical testing of all investigational substances. Clinical testing must be preceded by sufficient laboratory experiments, including, when appropriate, animal testing, to demonstrate a reasonable probability of success without undue risk. Such preliminary testing is implied by the Declaration of Helsinki, Article 1.7, which requires forgoing research involving human subjects unless "the hazards involved are believed to be predictable", and by Article 1.5, which requires that clinical testing "be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others."

Ideally, when benefits are intended for society but not for the subject, the subjects should be individuals who are fully capable of informed consent and who understand and accept the risks. Thus, unless there is specially strong justification, Phases 1 and 11 of vaccine testing and Phase 1 of drug testing should not involve subjects with limited capacity to consent or who are otherwise vulnerable. The requirement of the Declaration of Helsinki, Article 111.2, that "subjects should be volunteers-either healthy persons or patients for whom the experimental design is not related to the patient's illness" is not to be disregarded lightly.

In Phases 11 and 111 of drug testing and Phase 111 of vaccine testing, when benefits are intended for the subjects and they are reasonably likely to be realized, it is permissible to involve members of vulnerable groups and persons with limited capacity to consent.

However, as required by the Declaration of Helsinki, Article II.3, "every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method." Therefore, if there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified.

Ethical justification to begin a randomized clinical trial also meets the requirements of Article 11. 3. The therapies (or other interventions) to be compared must be regarded as equally advantageous to the prospective subjects: there should be no scientific evidence to establish the superiority of one over another. Moreover, no other intervention must be known to be superior to those being compared in the clinical trial, unless eligibility to participate is limited to persons who have been unsuccessfully treated with the other superior intervention or to persons who are aware of the other intervention and its superiority and have chosen not to accept it.

For each randomized clinical trial there should be a data and safety monitoring committee, responsible for monitoring the data obtained in the course of a study and for making recommendations to the sponsors and investigators about modifying or terminating the study, or about amending the informed-consent process or form. Such recommendations are made in response to the committee's detection of adverse events of which the nature, frequency or magnitude had not been anticipated by the investigators or sponsors as they planned the study, or of evidence that one of the therapies or preventive measures being tested in the clinical trial is superior to another. During the planning stage of a clinical trial, stopping-rules should be established to guide the data and safety monitoring committee in determining when it should recommend termination of the study.

National or local review. Review committees may be created under the aegis of national or local health administrations, national medical research councils or other nationally-representative bodies. In a highly centralized administration, a national review committee may be constituted for both the scientific and the ethical review of research protocols. In countries where medical research is not centrally directed, protocols are more effectively and conveniently reviewed from the ethical standpoint at a local or regional level. The competence of a local committee may be confined exclusively to a single research institution or may extend to all human-subject biomedical research undertaken within a defined geographical area. The basic responsibilities of local ethical review committees are twofold:

- to verify that all proposed interventions, and particularly the administration of drugs and vaccines or use of medical devices under development, have been assessed by a competent expert body as acceptably safe to be undertaken in human subjects; and
- to ensure that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice.

Committee membership. Local review committees should be so composed as to be able to provide complete and adequate review of the research activities referred to them. They should include physicians, scientists and other professionals, such as nurses, lawyers,

ethicists and clergy, as well as lay persons qualified to represent the cultural and moral values of the community. The membership should include both men and women. Committees that often review research directed at specific diseases or impairments, such as AIDS or paraplegia, should consider the advantages of including as members or consultants patients with such diseases or impairments. Similarly, committees that review research involving such vulnerable groups as children, students, aged persons or employees should consider the advantages of including representatives of, or advocates for, such groups. Membership should be rotated periodically with the aim of blending the advantages of experience with those of openness to cultural and scientific evolution. Independence from the investigators and avoidance of conflict of interest are maintained by excluding from the assessment of a proposal any member with a direct interest in the proposal.

Need for particularly stringent review requirements. The requirements of review committees should be particularly stringent in the case of proposed research involving children, pregnant and nursing women, persons with mental or behavioural disorders, communities unfamiliar with modern clinical concepts, and other vulnerable social groups, and in the case of invasive non-clinical research. In considering such proposals the review committee should be especially attentive in determining that selection of research subjects is both equitable (designed to distribute fairly the burdens and benefits of research) and likely to minimize risk to subjects.

Multicentre research. Some research projects are designed to be conducted in a number of sites in different communities or countries. Generally, to ensure that the results will be valid, the study must be conducted in an identical way at each of the different sites. Such studies include multicentre clinical trials, evaluation of health service programmes, and various kinds of epidemiological research. In such studies local ethical review committees must either accept or reject the protocol in its entirety; they must not impose requirements to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. In some such studies, scientific and ethical review may be facilitated by agreement among institutions to accept the results of review by a single review committee, whose members would include representatives of ethical review committees at each of the places in which the research is to be conducted.

Sanctions. Ethical review committees generally have no authority to impose sanctions on investigators who violate ethical standards in the conduct of research involving human subjects. However, they should be required to report to institutional or governmental authorities any serious or continuing noncompliance with ethical standards as they are reflected in protocols that they have approved. Failure to submit a protocol to the committee should be considered a violation of ethical standards.

Sanctions imposed by institutional, governmental, professional or other authorities possessing disciplinary power should be employed as a last resort. Preferred methods of control include cultivation of an atmosphere of mutual trust, and education and support to promote in investigators and in sponsors the capacity for ethical conduct of research.

Should sanctions become necessary, they should be directed at the noncompliant investigators or sponsors. They may include fines or suspension of eligibility to receive research funding, to use investigational therapies, or to practise medicine. Refusal to publish the results of research conducted unethically, as prescribed in the Declaration of Helsinki, Article 1.8, may be considered, as may refusal to accept unethically obtained data submitted in support of an application for drug registration. However, these sanctions deprive of benefit not only the errant investigator or sponsor but also that segment of society intended to benefit from the research; such possible consequences merit careful consideration.

Publications of reports of the results of research involving human subjects should include, when appropriate, a statement that the research was conducted in accordance with these guidelines. Departures, if any, from these guidelines should be explained and justified in the report submitted for publication.

Information to be provided by investigators. Whatever the procedure adopted for ethical review, such review should be based on a detailed protocol comprising:

- a clear statement of the research objectives, having regard to the present state of knowledge, and a justification for undertaking the investigation in human subjects;
- a precise description of all proposed interventions, including intended dosages of drugs and planned duration of treatment;
  - a description of plans to withdraw or withhold standard therapies in the course of the research;
- a description of the plans for statistical analysis of the study, which includes a calculation of the statistical power of the study, specifies the criteria for terminating the study, and demonstrates that the proper number of subjects will be recruited;
- the criteria determining admission and withdrawal of individual subjects, including full details of the procedure for seeking and obtaining informed consent;
- an account of any economic or other inducements to participate, such as offers of cash payments, gifts, or free services or facilities, and of any financial obligations assumed by the subjects, such as payment for medical services; and
- for research carrying more than minimal risk of physical injury, an account of plans, if any, to provide medical therapy for such injury and to provide compensation for research-related disability or death.

Information should also be included to establish:

- the safety of each proposed intervention and of any drug or vaccine to be tested, including the results of relevant laboratory and animal research;
- the anticipated benefits and the risks of participation;
- the means proposed to obtain individual informed consent or, when a prospective subject is not capable of informed consent, satisfactory assurance that proxy consent will be obtained from a duly authorized person and that the rights and welfare of each subject will be adequately protected;

- the identification of the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, investigators, research subjects and, when appropriate, the community;
- plans to inform subjects about harms and benefits during the study, and of the results of the study at its conclusion;
- an explanation of who will be involved in the research, their age, sex and circumstances, and, if any classes are excluded, the justification for the exclusion;
- justification for involving as research subjects persons with limited capacity to consent or members of vulnerable social groups;
- evidence that the investigator is qualified and experienced and is assured of adequate facilities for the safe and efficient conduct of the research;
- provisions that will be made for protecting the confidentiality of data; and,
- the nature of any other ethical considerations involved, together with an indication that the principles of the Declaration of Helsinki will be implemented.

Externally Sponsored Research

Guideline 15: Obligations of sponsoring and host countries

Externally sponsored research entails two ethical obligations:

- **An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should he no less exacting than they would be in the case of research carried out in that country.**
- **After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements.**

Commentary on Guideline 15

Definition. The term "externally sponsored research" refers to research undertaken in a host country but sponsored, financed, and sometimes wholly or partly carried out by an external international or national agency, with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country.

Ethical and scientific review. Committees in both the country of the sponsoring agency and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards. Special responsibilities may be assigned to review committees in the two countries when a sponsor or investigator in a developed country proposes to carry out research in a developing country. When the external sponsor is an international agency the research protocol must be reviewed according to its own independent ethical review procedures and standards.

Committees in the external sponsoring country or international agency have a special responsibility to determine whether the scientific methods are sound and suitable for the aims of the research, whether the drugs, vaccines or devices to be studied meet adequate standards of safety, whether there is sound justification for conducting the research in the host country rather than in the country of the external sponsoring agency, and that the proposed research does not in principle violate the ethical standards of the external sponsoring country or international organization.

Committees in the host country have the special responsibility to determine whether the goals of the research are responsive to the health needs and priorities of the host country. Moreover, because of their better understanding of the culture in which the research is proposed to be carried out, they have special responsibility for assuring the equitable selection of subjects and the acceptability of plans to obtain informed consent, to respect privacy, to maintain confidentiality, and to offer benefits that will not be considered excessive inducements to consent.

In short, ethical review in the external sponsoring country may be limited to ensuring compliance with broadly stated ethical standards, on the understanding that ethical review committees in the host country will have greater competence in reviewing the detailed plans for compliance in view of their better understanding of the cultural and moral values of the population in which the research is proposed to be conducted.

Research designed to develop therapeutic, diagnostic or preventive products. When externally sponsored research is initiated and financed by an industrial sponsor such as a pharmaceutical company, it is in the interest of the host country to require that the research proposal be submitted with the comments of a responsible authority of the initiating country, such as a health administration, research council, or academy of medicine or science.

Externally sponsored research designed to develop a therapeutic, diagnostic or preventive product must be responsive to the health needs of the host country. It should be conducted only in host countries in which the disease or other condition for which the product is indicated is an important problem. As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing. Exceptions to this general requirement should be justified and agreed to by all concerned parties before the research begins. Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study.

Obligations of external sponsors. An important secondary objective of externally sponsored collaborative research is to help develop the host country's capacity to carry out similar research projects independently, including their ethical review. Accordingly, external sponsors are expected to employ and, if necessary, train local individuals to

function as investigators, research assistants, or data managers or in other similar capacities. When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited. Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy. However, sponsors have an obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation is provided for death or disability occurring as a consequence of such injury (see Guideline 13 for a statement of the scope and limits of such obligations). Also, sponsors and investigators should refer for health care services subjects or prospective subjects who are found to have diseases unrelated to the research, and should advise prospective subjects who are rejected as research subjects because they do not meet health criteria for admission to the investigation to seek medical care. Sponsors are expected to ensure that research subjects and the communities from which they are recruited are not made worse off as a result of the research (apart from justifiable risks of research interventions) - for example, by the diversion of scarce local resources to research activities. Sponsors may disclose to the proper authorities in the host country information that relates to the health of the country or community, discovered in the course of a study.

External sponsors are expected to provide, as necessary, reasonable amounts of financial, educational and other assistance to enable the host country to develop its own capacity for independent ethical review of research proposals and to form independent and competent scientific and ethical review committees. To avoid conflict of interest, and to assure the independence of committees, such assistance should not be provided directly to the committees; rather funds should be made available to the host-country government or to the host research-institution.

Obligations of sponsors will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before research is begun. The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available, during and after the research, to the community from which the subjects are drawn and to the host country. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when relevant, the community from which subjects are to be drawn. The ethical review committee in the host country should determine whether any or all of these details should be made a part of the consent process.

Operational Guidelines for Ethics Committees That Review Biomedical Research

World Health Organization
Geneva
2000

PREFACE

The ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the WHO and ICH Guidelines for Good Clinical Practice. Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well-being of research participants are promoted and that the results of the investigations are credible.

All international guidelines require the ethical and scientific review of biomedical research alongside informed consent and the appropriate protection of those unable to consent as essential measures to protect the individual person and the communities who participate in research. For the purposes of these Guidelines, biomedical research includes research on pharmaceuticals, medical devices, medical radiation and imaging, surgical procedures, medical records, and biological samples, as well as epidemiological, social, and psychological investigations.

These Guidelines are intended to facilitate and support ethical review in all countries around the world. They are based on a close examination of the requirements for ethical review as established in international guidelines, as well as on an evaluation of existing practices of ethical review in countries around the world. They do not, however, purport to replace the need for national and local guidelines for the ethical review of biomedical research, nor do they in-tend to supersede national laws and regulations. The majority of biomedical research has been predominantly motivated by concern for the benefit of already privileged communities. This is reflected by the fact that the WHO estimates that 90% of the resources devoted to research and development on medical problems are applied to diseases causing less than 10% of the present global suffering. The establishment of international guidelines that assist in strengthening the capacity for the ethical review of bio-medical research in all countries contributes to redressing this imbalance.

1 OBJECTIVE

The objective of these Guidelines is to contribute to the development of quality and consistency in the ethical review of biomedical research. The Guidelines are intended to complement existing laws, regulations, and practices, and to serve as a basis upon which ethics committees (ECs) can develop their own specific written procedures for their functions in biomedical research. In this regard, the Guidelines establish an international standard for ensuring quality in ethical review. The Guidelines should be used by national
and local bodies in developing, evaluating, and progressively refining standard operating procedures for the ethical review of biomedical research.

2 THE ROLE OF AN EC

The purpose of an EC in reviewing biomedical research is to contribute to safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants. A cardinal principle of research involving human participants is 'respect for the dignity of persons'. The goals of research, while important, should never be permitted to override the health, well-being, and care of research participants. ECs should also take into consideration the principle of justice. Justice requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture, and ethnic considerations.

ECs should provide independent, competent, and timely review of the ethics of proposed studies. In their composition, procedures, and decision-making, ECs need to have independence from political, institutional, professional, and market influences. They need similarly to demonstrate competence and efficiency in their work.

ECs are responsible for carrying out the review of proposed research before the commencement of the research. They also need to ensure that there is regular evaluation of the ethics of ongoing studies that received a positive decision.

ECs are responsible for acting in the full interest of potential research participants and concerned communities, taking into account the interests and needs of the researchers, and having due regard for the requirements of relevant regulatory agencies and applicable laws.

3 ESTABLISHING A SYSTEM OF ETHICAL REVIEW

Countries, institutions, and communities should strive to develop ECs and ethical review systems that ensure the broadest possible coverage of protection for potential research participants and con-tribute to the highest attainable quality in the science and ethics of
biomedical research. States should promote, as appropriate, the establishment of ECs at the national, institutional, and local levels that are independent, multi-disciplinary, multi-sectorial, and pluralistic in nature. ECs require administrative and financial support.

Procedures need to be established for relating various levels of re-view in order to ensure consistency and facilitate cooperation. Mechanism for cooperation and communication need to be developed between national committees and institutional and local committees. These mechanisms should ensure clear and efficient communication.
They should also promote the development of ethical review within a country as well as the ongoing education of members of ethics committees. In addition, procedures need to be established for the review of biomedical research protocols carried out at more than one site in a country or in more than one country. A network of ethical review should be established at the regional, national, and local levels that ensures the highest competence in biomedical review while also guaranteeing input from all levels of the community.

4 CONSTITUTING AN EC

ECs should be constituted to ensure the competent review and evaluation of all ethical aspects of the research projects they receive and to ensure that their tasks can be executed free from bias and influence that could affect their independence.

ECs should be multidisciplinary and multi-sectorial in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community.

ECs should be established in accordance with the applicable laws and regulations of the country and in accordance with the values and principles of the communities they serve.

ECs should establish publicly available standard operating procedures that state the authority under which the committee is established, the functions and duties of the EC, membership requirements, the terms of appointment, the conditions of appointment, the offices, the structure of the secretariat, internal procedures, and the quorum requirements. ECs should act in accordance with their written operating procedures.

It may be helpful to summarize the activities of the EC in a regular (annual) report.

4.1 Membership Requirements

Clear procedures for identifying or recruiting potential EC members should be established. A statement should be drawn up of the requirements for candidacy that includes an outline of the duties and responsibilities of EC members.

Membership requirements should be established that include the following:

4.1.1 the name or description of the party responsible for making appointments;

4.1.2 the procedure for selecting members, including the method for appointing a member (e.g., by consensus, by majority vote, by direct appointment);

4.1.3 conflicts of interest should be avoided when making appointments, but where unavoidable there should be transparency with regard to such interests.

A rotation system for membership should be considered that allows for continuity, the development and maintenance of expertise within the EC, and the regular input of fresh ideas and approaches.

4.2 Terms of Appointment

Terms of appointment should be established that include the following:

4.2.1 the duration of an appointment,

4.2.2 the policy for the renewal of an appointment,

4.2.3 the disqualification procedure,

4.2.4 the resignation procedure,

4.2.5 the replacement procedure.

4.3 Conditions of Appointment

A statement of the conditions of appointment should be drawn up that includes the following:

4.3.1 a member should be willing to publicize his/her full name, profession, and affiliation;

4.3.2 all reimbursement for work and expenses, if any, within or related to an EC should be recorded and made available to the public upon request;

4.3.3 a member should sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; in addition, all EC administrative staff should sign a similar confidentiality agreement.

4.4 Offices

ECs should establish clearly defined offices for the good functioning of ethical review. A statement is required of the officers within the EC (e.g., chairperson, secretary), the requirements for holding each office, the terms and conditions of each office, and the duties and responsibilities of each office (e.g., agenda, minutes, notification of decisions). Clear procedures for selecting or appointing officers should be established.

In addition to the EC officers, an EC should have adequate support staff for carrying out its responsibilities.

4.5 Quorum Requirements

ECs should establish specific quorum requirements for reviewing and deciding on an application. These requirements should include:

4.5.1 the minimum number of members required to compose a quorum (e.g., more than half the members);

4.5.2 the professional qualifications requirements (e.g., physician, lawyer, statistician, paramedical, layperson) and the distribution of those requirements over the quorum; no quorum should consist entirely of members of one profession or one gender; a quorum should include at least one member whose primary area of expertise is in a non-scientific area, and at least one member who is independent of the institution/research site.

4.6 Independent Consultants

ECs may call upon, or establish a standing list of, independent consultants who may provide special expertise to the EC on proposed research protocols. These consultants may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities, patients, or special interest groups. Terms of reference for independent consultants should be established.

4.7 Education for EC Members

EC members have a need for initial and continued education regarding the ethics and science of biomedical research. The conditions of appointment should state the provisions available for EC members to receive introductory training in the work of an EC as well as ongoing opportunities for enhancing their capacity for ethical review. These conditions should also include the

requirements or expectations regarding the initial and continuing education of EC members. This education may be linked to co-operative arrangements with other ECs in the area, the country, and the region, as well as other opportunities for the initial and continued training of EC members.

5 SUBMITTING AN APPLICATION

ECs are responsible for establishing well-defined requirements for submitting an application for review of a biomedical research project. These requirements should be readily available to prospective applicants.

5.1 Application

An application for review of the ethics of proposed biomedical research should be submitted by a qualified researcher responsible for the ethical and scientific conduct of the research.

5.2 Application Requirements

The requirements for the submission of a research project for ethical review should be clearly described in an application procedure. These requirements should include the following:

5.2.1 the name(s) and address(es) of the EC secretariat or member(s) to whom the application material is to be submitted;

5.2.2 the application form(s);

5.2.3 the format for submission;

5.2.4 the documentation (see 5.3);

5.2.5 the language(s) in which (core) documents are to be submitted;

5.2.6 the number of copies to be submitted;

5.2.7 the deadlines for submission of the application in relation to review dates;

5.2.8 the means by which applications will be acknowledged, including the communication of the incompleteness of an application;

5.2.9 the expected time for notification of the decision following review;

5.2.10 the time frame to be followed in cases where the EC requests supplementary information or changes to documents from the applicant;

5.2.11 the fee structure, if any, for reviewing an application;

5.2.12 the application procedure for amendments to the protocol, the recruitment material, the potential research participant information, or the informed consent form.

5.3 Documentation

All documentation required for a thorough and complete review of the ethics of proposed research should be submitted by the applicant. This may include, but is not limited to,

5.3.1 signed and dated application form;

5.3.2 the protocol of the proposed research (clearly identified and dated), together with supporting documents and annexes;

5.3.3 a summary (as far as possible in non-technical language), synopsis, or diagrammatic representation ('flowchart') of the protocol;

5.3.4 a description (usually included in the protocol) of the ethical considerations involved in the research;

5.3.5 case report forms, diary cards, and other questionnaires intended for research participants;

5.3.6 when the research involves a study product (such as a pharmaceutical or device under investigation), an adequate summary of all safety, pharmacological, pharmaceutical, and toxicological data available on the study product, together with a summary of clinical experience with the study product to date (e.g., recent investigator's brochure, published data, a summary of the product's characteristics);

5.3.7 investigator(s)'s curriculum vitae (updated, signed, and dated);

5.3.8 material to be used (including advertisements) for the recruitment of potential research participants;

5.3.9 a description of the process used to obtain and document consent;

5.3.10 written and other forms of information for potential research participants (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages;

5.3.11 informed consent form (clearly identified and dated) in the language(s) understood by the potential research participants and, when required, in other languages;

5.3.12 a statement describing any compensation for study participation (including expenses and access to medical care) to be given to research participants;

5.3.13 a description of the arrangements for indemnity, if applicable;

5.3.14 a description of the arrangements for insurance coverage for research participants, if applicable;

5.3.15 a statement of agreement to comply with ethical principles set out in relevant guidelines;

5.3.16 all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of modification(s) to the protocol made on that account. The reasons for previous negative decisions should be provided.

6 REVIEW

All properly submitted applications should be reviewed in a timely fashion and according to an established review procedure.

6.1 Meeting Requirements

ECs should meet regularly on scheduled dates that are announced in advance. The meeting requirements should include the following:

6.1.1 meetings should be planned in accordance with the needs of the workload;

6.1.2 EC members should be given enough time in advance of the meeting to review the relevant documents;

6.1.3 meetings should be minuted; there should be an approval procedure for the minutes;

6.1.4 the applicant, sponsor, and/or investigator may be invited to present the proposal or elaborate on specific issues;

6.1.5 independent consultants may be invited to the meeting or to provide written comments, subject to applicable confidentiality agreements.

6.2 Elements of the Review

The primary task of an EC lies in the review of research proposals and their supporting documents, with special attention given to the informed consent process, documentation, and the suitability and feasibility of the protocol. ECs need to take into account prior scientific reviews, if any, and the requirements of applicable laws and regulations. The following should be considered, as applicable:

6.2.1 Scientific Design and Conduct of the Study

6.2.1.1 the appropriateness of the study design in relation to the objectives of the study, the statistical methodology (including sample size calculation), and the potential for reaching sound conclusions with the smallest number of research participants;

6.2.1.2 the justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants and the concerned communities;

6.2.1.3 the justification for the use of control arms;

6.2.1.4 criteria for prematurely withdrawing research participants;

6.2.1.5 criteria for suspending or terminating the research as a whole;

6.2.1.6 the adequacy of provisions made for monitoring and auditing the conduct of the research, including the constitution of a data safety monitoring board (DSMB);

6.2.1.7 the adequacy of the site, including the supporting staff, available facilities, and emergency procedures;

6.2.1.8 the manner in which the results of the research will be reported and published;

6.2.2 Recruitment of Research Participants

6.2.2.1 the characteristics of the population from which the research participants will be drawn (including gender, age, literacy, culture, economic status, and ethnicity);

6.2.2.2 the means by which initial contact and recruitment is to be conducted;

6.2.2.3 the means by which full information is to be conveyed to potential research participants or their representatives;

6.2.2.4 inclusion criteria for research participants;

6.2.2.5 exclusion criteria for research participants;

6.2.3 Care and Protection of Research Participants

6.2.3.1 the suitability of the investigator(s)'s qualifications and experience for the proposed study;

6.2.3.2 any plans to withdraw or withhold standard therapies for the purpose of the research, and the justification for such action;

6.2.3.3 the medical care to be provided to research participants during and after the course of the research;

6.2.3.4 the adequacy of medical supervision and psycho-social support for the research participants;

6.2.3.5 steps to be taken if research participants voluntarily withdraw during the course of the research;

6.2.3.6 the criteria for extended access to, the emergency use of, and/or the compassionate use of study products;

6.2.3.7 the arrangements, if appropriate, for informing the research participant's general practitioner (family doctor), including procedures for seeking the participant's consent to do so;

6.2.3.8 a description of any plans to make the study product available to the research participants following the research;

6.2.3.9 a description of any financial costs to research participants;

6.2.3.10 the rewards and compensations for research participants (including money, services, and/or gifts);

6.2.3.11 the provisions for compensation/treatment in the case of the injury/disability/death of a research participant attributable to participation in the research;

6.2.3.12 the insurance and indemnity arrangements;

6.2.4 Protection of Research Participant Confidentiality

6.2.4.1 a description of the persons who will have access to personal data of the research participants, including medical records and biological samples;

6.2.4.2 the measures taken to ensure the confidentiality and security of personal information concerning research participants;

6.2.5 Informed Consent Process

6.2.5.1 a full description of the process for obtaining informed consent, including the identification of those responsible for obtaining consent;

6.2.5.2 the adequacy, completeness, and understandability of written and oral information to be given to the research participants, and, when appropriate, their legally acceptable representative(s);

6.2.5.3 clear justification for the intention to include in the research individuals who cannot consent, and a full account of the arrangements for obtaining consent or authorization for the participation of such individuals;

6.2.5.4 assurances that research participants will receive information that becomes available during the course of the research relevant to their participation (including their rights, safety, and well-being);

12.6.2.5.5 the provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project;

6.2.6 Community Considerations

6.2.6.1 the impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn;

6.2.6.2 the steps taken to consult with the concerned communities during the course of designing the research;

6.2.6.3 the influence of the community on the consent of individuals;

6.2.6.4 proposed community consultation during the course of the research;

6.2.6.5 the extent to which the research contributes to capacity building, such as the enhancement of local healthcare, research, and the ability to respond to public health needs;

6.2.6.6 a description of the availability and affordability of any successful study product to the concerned communities following the research;

6.2.6.7 the manner in which the results of the research will be made available to the research participants and the concerned communities.

6.3 Expedited Review

ECs should establish procedures for the expedited review of research proposals. These procedures should specify the following:

6.3.1 the nature of the applications, amendments, and other considerations that will be eligible for expedited review;

6.3.2 the quorum requirement(s) for expedited review;

6.3.3 the status of decisions (e.g., subject to confirmation by full EC or not).

7 DECISION-MAKING

In making decisions on applications for the ethical review of biomedical research, an EC should take the following into consideration:

7.1 a member should withdraw from the meeting for the decision procedure concerning an application where there arises a conflict of interest; the conflict of interest should be indicated to the chairperson prior to the review of the application and recorded in the minutes;

7.2 a decision may only be taken when sufficient time has been allowed for review and discussion of an application in the absence of non-members (e.g., the investigator, representatives of the sponsor, independent consultants) from the meeting, with the exception of EC staff;

7.3 decisions should only be made at meetings where a quorum (as stipulated in the EC's written operating procedures) is present;

7.4 the documents required for a full review of the application should be complete and the relevant elements mentioned above (see 6.2) should be considered before a decision is made;

7.5 only members who participate in the review should participate in the decision;

7.6 there should be a predefined method for arriving at a decision (e.g., by consensus, by vote); it is recommended that decisions be arrived at through consensus, where possible; when a consensus appears unlikely, it is recommended that the EC vote;

7.7 advice that is non-binding may be appended to the decision;

7.8 in cases of conditional decisions, clear suggestions for re-vision and the procedure for having the application re-reviewed should be specified;

7.9 a negative decision on an application should be supported by clearly stated reasons.

8 COMMUNICATING A DECISION

A decision should be communicated in writing to the applicant according to EC procedures, preferably within two weeks' time of the meeting at which the decision was made. The communication of the decision should include, but is not limited to, the following:

8.1 the exact title of the research proposal reviewed;

8.2 the clear identification of the protocol of the proposed research or amendment, date and version number (if applicable) on which the decision is based;

8.3 the names and (where possible) specific identification numbers (version numbers/dates) of the documents reviewed, including the potential research participant information sheet/material and informed consent form;

8.4 the name and title of the applicant;

8.5 the name of the site(s);

8.6 the date and place of the decision;

8.7 the name of the EC taking the decision;

8.8 a clear statement of the decision reached;

8.9 any advice by the EC;

8.10 in the case of a conditional decision, any requirements by the EC, including suggestions for revision and the procedure for having the application re-reviewed;

8.11 in the case of a positive decision, a statement of the responsibilities of the applicant; for example, confirmation of the acceptance of any requirements imposed by the EC; submission of progress report(s); the need to notify the EC in cases of protocol amendments (other than amendments involving only logistical or administrative aspects of the study); the need to notify the EC in the case of amendments to the recruitment material, the potential research participant information, or the informed consent form; the need to report serious and unexpected adverse events related to the conduct of the study; the need to report unforeseen circumstances, the termination of the study, or significant decisions by other ECs; the information the EC expects to receive in order to perform ongoing review; the final summary or final report;

8.12 the schedule/plan of ongoing review by the EC;

8.13 in the case of a negative decision, clearly stated reason(s) for the negative decision;

8.14 signature (dated) of the chairperson (or other authorized person) of the EC.

9 FOLLOW-UP

ECs should establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research. The ongoing lines of communication between the EC and the applicant should be clearly specified. The follow-up procedure should take the following into consideration:

9.1 the quorum requirements, the review procedure, and the communication procedure for follow-up reviews, which may vary from the requirements and procedures for the initial decision on an application;

9.2 the follow-up review intervals should be determined by the nature and the events of research projects, though each protocol should undergo a follow-up review at least once a year;

9.3 the following instances or events require the follow-up review of a study:

a. any protocol amendment likely to affect the rights, safety, and/or well-being of the research participants or the conduct of the study;
b. serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies;
c. any event or new information that may affect the benefit/risk ratio of the study;

9.4 a decision of a follow-up review should be issued and communicated to the applicant, indicating a modification, suspension, or termination of the EC's original decision or confirmation that the decision is still valid;

9.5 in the case of the premature suspension/termination of a study, the applicant should notify the EC of the reasons for suspension/termination; a summary of results obtained in a study prematurely suspended/terminated should be communicated to the EC;

9.6 ECs should receive notification from the applicant at the time of the completion of a study;

9.7 ECs should receive a copy of the final summary or final report of a study.

10 DOCUMENTATION AND ARCHIVING

All documentation and communication of an EC should be dated, filed, and archived according to written procedures. A statement is required defining the access and retrieval procedure (including authorized persons) for the various documents, files, and archives.
It is recommended that documents be archived for a minimum period of 3 years following the completion of a study. Documents that should be filed and archived include, but are not limited to,

10.1 the constitution, written standard operating procedures of the EC, and regular (annual) reports;

10.2 the curriculum vitae of all EC members;

10.3 a record of all income and expenses of the EC, including allowances and reimbursements made to the secretariat and EC members;

10.4 the published guidelines for submission established by the EC;

10.5 the agenda of the EC meetings;

10.6 the minutes of the EC meetings;

10.7 one copy of all materials submitted by an applicant;

10.8 the correspondence by EC members with applicants or concerned parties regarding application, decision, and follow-up;

10.9 a copy of the decision and any advice or requirements sent to an applicant;

10.10 all written documentation received during the follow-up;

10.11 the notification of the completion, premature suspension, or premature termination of a study;

10.12 the final summary or final report of the study.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these Guidelines. The terms may have different meanings in other contexts.

advice
Non-binding considerations adjoined to a decision intended to pro-vide ethical assistance to those involved in the research.

applicant
A qualified researcher undertaking the scientific and ethical responsibility for a research project, either on his/her own behalf or on behalf of an organization/firm, seeking a decision from an ethics committee through formal application.

community
A community is a group of people understood as having a certain identity due to the sharing of common interests or to a shared proximity. A community may be identified as a group of people living in the same village, town, or country and, thus, sharing geographical proximity. A community may be otherwise identified as a group of people sharing a common set of values, a common set of interests, or a common disease.

conflict of interest
A conflict of interest arises when a member (or members) of the EC holds interests with respect to specific applications for review that may jeopardize his/her (their) ability to provide a free and independent evaluation of the research focused on the protection of the research participants. Conflicts of interests may arise when an EC member has financial, material, institutional, or social ties to the research.

decision
The response, (either positive, conditional or negative), by an EC to an application following the review in which the position of the EC on the ethical validity of the proposed study is stated.

investigator
A qualified scientist who undertakes scientific and ethical responsibility, either on his/her own behalf or on behalf of an organization/firm, for the ethical and scientific integrity of a research project at a specific site or group of sites. In some instances a coordinating or principal investigator may be appointed as the responsible leader of a team of subinvestigators.

protocol
A document that provides the background, rationale, and objective(s) of a biomedical research project and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.

protocol amendment

A written description of a change to, or formal clarification of, a protocol.

requirements
In the context of decisions, requirements are binding elements that express ethical considerations whose implementation the ethics committee requires or views as obligatory in pursuing the research.

research participant
An individual who participates in a biomedical research project, either as the direct recipient of an intervention (e.g., study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, or a person with a condition unrelated to the research carried out who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

sponsor
An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a research project.

SUPPORTING DOCUMENTS

Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subject*s. Geneva 1993.

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Council of Europe. *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicin*e. European Treaty Series – No. 164. Oviedo, 4 April 1997.

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World Health Organization (WHO). Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. Annex 3 of *The Use of Essential Drug*s. Sixth Report of the WHO Expert Committee. Geneva: World Health Organization, 1995: 97-137.

World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subject*s. Adopted by the 18 th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29 th World Medical Assembly, Tokyo, Japan, October 1975; the 35 th World Medical 23.Assembly, Venice, Italy, October 1983; the 41 st World Medical Assembly, Hong Kong, September 1989; and the 48 th General Assembly, Somerset West, Republic of South Africa, October 1996.

World Medical Association, *Declaration of Lisbon on the Rights of the Patien*t. Adopted by the 34 th World Medical Assembly, Lisbon, Portugal, September/October 1981 and amended by the 47 th General Assembly, Bali, Indonesia, September 1995.

Operational Guidelines for
Ethics Committees Reviewing
Biomedical Research
UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases
(TDR)

Committees

International Working Party

*Solomon Benata*r, South Africa
*Chifumbe Chint*u, Zambia
*Francis P. Crawle*y, Belgium (Chairman)
Dafna Feinholz, Mexico
*Christine Grad*y, USA
*Dirceau Grec*o, Brazil
*Hakima Himmic*h, Morocco
*Andrew Kitu*a, Tanzania
*Olga Kuba*r, Russia
*Mary Ann Lansan*g, Philippines
*Reidar Li*e, Norway
*Vasantha Muthuswam*y, India
*Renzong Qi*u, China
*Judit Sándo*r, Hungary

Secretariat

*Juntra Karbwan*g, TDR WHO (Project Coordinator)
*Howard Enger*s, TDR WHO
*David Griffi*n, WHO
*Tikki Pan*g, WHO
*Daniel Wikle*r, WHO
*Myint Htw*e, SEARO, WHO
*Chen Ke*n, WPRO, WHO
*Abdelhay Mechba*l, EMRO, WHO
*Antoine Kabor*é, AFRO, WHO
*Alberto Pellegrini-Filh*o, AMRO, WHO
*Mariam Maluw*a, UNAIDS
*Claire Patto*u, UNAIDS
*John Bryan*t, CIOMS
*Ryuichi Id*a, UNESCO
*Delon Huma*n, WMA

Consultation Partners

*Odette Morin Carpentie*r, International Federation of Pharmaceutical Manufacturers' Associations
*Elaine Esbe*r, Food and Drug Administration, USA and FDA Representative to the International Conference on Harmonization

*Nadia Tornieport*h, SmithKline Beecham Biologics
*Wen Kilam*a, African Malaria Vaccine Testing Network
*Robert Eis*s, National Institutes of Health, USA
*Melody H. Li*n, Office for Protection from Research Risks (OPRR), USA
*Dixie Snide*r, Centers for Disease Control and Prevention, USA
*Henry Dinsdal*e, National Council on Ethics in Human Research, Canada
*Elaine Gad*d, Steering Committee on Bioethics, Council of Europe
*Laurence Cordie*r, European Commission
*Fergus Sweene*y, European Medicines Evaluation Agency
*Betty Dode*t, Fondation Marcel Mérieux
*Kries De Clerc*k, European Forum for Good Clinical Practice
*Jean-Marc Husso*n, International Federation of Associations of Pharmaceutical Physicians
*Denis Lacomb*e, European Organization for Research & Treatment of Cancer
*Frank Well*s, Faculty of Pharmaceutical Medicine, UK
*Frédérick Ga*y, Regional Malaria Control Programme in Cambodia,
Laos, and Vietnam, European Commission

BACKGROUND

The *Operational Guidelines for Ethics Committees That Review Biomedical Research* is the result of a wide international consultation begun in August 1999 at A Seminar on the Ethical Review of Clinical Research in Asian & Western Pacific Countries organized
by TDR WHO in Chiang Mai, Thailand. The participants at the seminar expressed a need for international guidance on the constitution and operation of ethics committees. The first draft of these *Guidelines* was discussed at a workshop for members of African Ethical Review Committees organized by TDR WHO and the African Malaria Vaccine Testing Network in Arusha, Tanzania, on 5 November 1999. The draft was subsequently presented to an Interim Meeting of the Forum for Ethical Review Committees in the Asian & Western Pacific Regions (FERCAP) in Bethesda, MD, USA, on 9 November 1999. It was also distributed for consultation at the Global Forum for Bioethics in Research organized by the NIH and WHO in Bethesda on 7-10 November 1999.
Following these initial consultations the *Guidelines* were redrafted and widely distributed for comment.

Further development of these *Guidelines* was carried out under the auspices of a Secretariat composed of representatives from WHO, UNAIDS, CIOMS, UNESCO, and the WMA. Responsibility for drafting these *Guidelines* was given to an International Drafting Committee of 14 experts from various continents representing a wide range of disciplines in biomedical research and bioethics. The consultation process was carried out through representatives from the African Malaria Vaccine Testing Network, Council of Europe, European Commission, European Medicines Evaluation Agency, National Institutes of Health (USA), Food & Drug Administration (USA), Office for Protection from Research Risks (USA), Centers for Disease Control and Prevention (USA), National Council on Ethics in Human Research (Canada), Faculty of Pharmaceutical
Medicine (United Kingdom), European Organization for Research & Treatment of Cancer, International Federation of Pharmaceutical Physicians, Foundation Marcel Mérieux, International Federation of Pharmaceutical Manufacturers' Associations, International Conference on Harmonization, and European Forum for Good Clinical
Practice. In addition, the draft text was widely distributed to organizations of ethics committees in Europe and the United States as well as to experts in the field of biomedical research ethics. On 2 January 2000 a new draft was prepared and distributed to the members of the Drafting Working Party, the Secretariat, and the Consultation

Partners as well as to other parties who had commented or expressed an interest.

Following on the reception of a wide range of detailed comments from around the world, the text was then widely discussed at a Meeting on Guidelines and Standard Operating Procedures for Ethical Review Committees held in Bangkok on 10-12 January 2000.
Participants in this meeting were drawn from the regions of Africa, Asia, Latin America, North America, and Europe, from international organizations, (including WHO, UNAIDS, UNESCO, CIOMS, EFGCP, and IFPMA), and from universities and research institutions. A final deliberation took place at a Drafting Meeting held on 13 January 2000 in Bangkok. Following the Drafting Meeting a final set of comments were solicited and integrated into the final document.

The purpose of this wide consultative process was to ensure extensive input while fostering the sharing of knowledge from developing and developed countries alongside organizations and institutions with varying degrees of experience and expertise. This process also help to prepare for the dissemination of the final text through an international process of capacity building that would strengthen national and local infrastructures for ethical review throughout the world.

The *Operational Guidelines for Ethics Committees That Review Biomedical Research* are proposed by the WHO and CIOMS as a support for improving the organization, quality, and standards of ethical review around the world. These *Guidelines* take into account current practices while suggesting guidance for a harmonized state-of-the-art approach.

Comments and suggestions on all aspects of these guidelines are welcome for consideration in future revisions of this document. Please correspond with:

Dr Juntra Karbwang
Clinical Coordinator
Product Research and Development
TDR/CDS/WHO
CH-1211 Geneva 27
Switzerland
Tel (41) 22 791 3867/8
Fax (41) 22 791 4854
E-mail: karbwangj@who.ch

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa,
October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the

health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient,

must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes[1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.[2] By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.[3]

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness

or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician

for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted,

inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires

those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a

therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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[1] Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2] Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving the intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3] Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.