Research Ethics Training Curriculum

Second Edition

NATIONAL INSTITUTES OF HEALTH

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Research Ethics Training Curriculum, Second Edition
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INTRODUCTION TO THE SECOND EDITION

The *Research Ethics Training Curriculum* (RETC) developed by FHI was first published in the spring of 2001. Since that time there has been an evolution of thinking about research ethics, not only within FHI but also within the global research community. Also, experience gained through trainings using the RETC, the review of research by the FHI Protection of Human Subjects Committee, and FHI's experience in implementing a global research portfolio compelled us to undertake the writing of a second edition.

Since 2001, some basic research ethics concepts have been expanded. This includes the vision of the three basic research ethics principles—respect, beneficence, and justice—going beyond the individual research participant to include entire communities where the research will be conducted. Of particular importance is the recognition that communities should be involved in the design and conduct of such research. Also, the concept of informed consent as an empowerment process continuing throughout the duration of the research is now firmly established. These and other new concepts are included in this second edition.

In the years since the publication of the first edition of the curriculum, FHI has conducted numerous trainings throughout the world using the RETC. We have learned a great deal and received many useful recommendations and suggestions, many of which have been included in this edition. We are very grateful to all who provided us with their invaluable advice.

One aspect that has not changed in this edition is our assertion that the fundamental ethical principles must continue to guide the design and implementation of research involving human participants. We further assert that these principles must be considered universal, transcending geographic, cultural, economic, legal and political boundaries. We acknowledge that the availability of resources needed to maintain these principles is not optimal. These limitations are more profound in developing countries, where the resources available for the operation of local Research Ethics Committees are often insufficient, potentially affecting the level of protection of research participants. We have also learned the importance of translating these principles into national or local guidelines that describe the processes that must be followed to actually protect the research participants.

This RETC has been developed for an international audience of researchers and Research Ethics Committee members who:

- Design or implement research that includes human participants
- Conduct reviews of the ethical aspects of research

The RETC provides a basic and accessible level of training appropriate for individuals from different professional backgrounds and world regions. It provides:

- An overview of the main ethical principles to be considered in the development and conduct of research involving human participants

- Guidance to assist researchers in designing studies that are respectful of local cultures, regulations, and expectations
- Case studies for considering real-world examples of ethical issues
- Ancillary reference documents on modern perspectives that shape the research ethics field

The promulgation of the principles of research ethics and the creation of national and international regulations and guidelines are the result of abuses in the past and in the present. Today, a great amount of attention is directed to improving the level of protections provided to research participants. Internationally accepted standards for research ethics help ensure that research conducted at the local level meets international expectations. Adhering to international norms validates the goodwill and trust invested by the participants.

It is essential that researchers familiarize themselves with the subject matter in this curriculum. Understanding current attitudes about research ethics and the events that shaped them will help each researcher move toward the goal symbolized by the lotus flower—purity and perfection in each research study.

The Lotus Flower

Another element retained from the original *Research Ethics Training Curriculum* is the lotus flower, which we use to symbolize the fundamental ethical elements. In many cultures, the image of the lotus flower represents **purity and perfection.** Through this curriculum, we challenge the research community to aspire to a pure and perfect research design—the foundation on which ethical research is developed and implemented.

We acknowledge that each research design, like each lotus flower, will be unique in that it will be:

- Specific to the study's design and research objectives
- Relevant to the local research environment
- Respectful of local culture

How to Use This Curriculum

This *Research Ethics Training Curriculum* is designed to engage the learner. Adult learning and retention improves with active participation by the learner. The RETC can be used as either an interactive, self-study program or as a participatory, group training experience. Individual learners can expect to spend a minimum of four hours completing the curriculum. Due to the number of suggested activities and case studies, it will generally take longer to complete the curriculum in a group setting; however, it can typically be covered in an eight-hour day. We recommend using the curriculum flexibly, without strict time limits. Sections such as the principles of research ethics, informed consent, and the responsibilities of Research Ethics Committees may generate much discussion by participants and may require longer periods of time.

The curriculum is divided into four sections:

- Contents

- Case Studies
- Evaluations
- Additional Resources

The *Contents* section is composed of illustrative slides and narrative text. Learner/ Facilitator Notes contain interactive questions or activities designed to stimulate further discussion of topics. Take the time to think about or to even write down your ideas about these questions or activities. If you are facilitating group training, ask the group to call out or write on flip charts the answers prompted by the Learner/Facilitator Notes.

The *Case Studies* section highlights issues in international research ethics and presents thought-provoking questions. In the original curriculum, the case studies focused on ethical issues in reproductive health research and were based on actual situations encountered by researchers at FHI. In the second edition, we have expanded the selection to include studies in other research areas and conducted by various organizations.

Several of these case studies are incorporated into the *Contents* section of the curriculum in order to emphasize key ideas. The additional case studies are included in the *Case Studies* section and may be interchanged according to local interests or to make the curriculum more interesting over repeated trainings.

The *Evaluations* section includes a 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 curriculum evaluation form to FHI, as noted below.

The *Additional Resources* section, under *Basic Research Ethics Documents* contains websites that will provide direct access to the full text of the following documents: The Belmont Report, the 2008 Declaration of Helsinki, the 2001 CIOMS International Guidelines for Biomedical Research Involving Human Subjects, the WHO Operational Guidelines for Ethics Committees that Review Biomedical Research and the U.S. Code of Federal Regulations. This section also provides a list of useful internet sites, and a suggested bibliography."

Getting Started
After reading this introduction, continue to the *Contents* section. First-time users should follow the sections sequentially. Do not rush; take time to consider the supplementary activities and case studies.

Once you complete the RETC, you will be prompted to complete the post-test. When you have finished all sections of the curriculum and the post-test, complete the curriculum evaluation found in the *Evaluations* section.

Certificate of Completion
Everyone that successfully completes the RETC is elegible to receive a certificate of completion from FHI's Office of International Research Ethics (OIRE).

Individuals completing the training online will have to: 1) take the post-test, 2) obtain at least an 80% grade, 3) submit the curriculum evaluation form, and 4) receive the certificate. FHI will issue immediately an electronic copy of the certificate that needs to be completed by the trainee who adds his full name and date of completion.

In group trainings, facilitators have the option of providing a certificate issued by the local institution sponsoring the training. Facilitators also have the option of requesting an electronic version of the certificiate to be printed and completed locally. Facilitators should provide printed evaluation forms for group training that are to be completed by trainees and sent to FHI.

Completed curriculum evaluations are submitted electronically to ethics@fhi.org. Paper submissions should be sent to:

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

Paper submission must include complete contact information, including e-mail address, so that FHI can send your certificate of completion. *Be sure that your mailing address is complete—include the name of your country!*

Contact Information
You may 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!

Facilitators

Guidelines for Group Training

The *Research Ethics Training Curriculum* is designed to engage the learner. Adult learning and retention improve when the learner participates actively. **We recommend that Group Facilitators complete the self-study section of the curriculum to prepare for the group training.**

The curriculum contains these print and projection tools in Adobe PDF format for use in group training:

- Color Slides for Online Presentation
- Case Studies
- Evaluations

Group training can typically be covered in an eight-hour day. We recommend using the curriculum flexibly, without strict time limits, according to local circumstances. A limit of 40 participants is recommended.

Color Slides for Online Presentation are for projection from a computer.

The text under each slide in the *Contents section, called the slide note,* provides the basic information to be presented. On some slides, the slide note is followed by a shaded box labeled **Learner/Facilitator Note.** These notes contain suggested interactive questions or activities.

The *Case Studies* section provides real-life health research studies followed by thought-provoking questions. The case studies are based on actual situations encountered by researchers at FHI and other leading research organizations worldwide and help anchor the curriculum to the reality of designing, implementing, and reviewing research studies. Some of the cases are included in the *Contents section*, and some are only in the *Case Study* section. **The Group Training Facilitator must carefully review the *Note to the Facilitator* at the beginning of the *Case Studies* section.**

The *Evaluations* section includes a post-test and c*urriculum evaluation form.* In order to receive a certificate of completion, follow the instructions in the *Certificate of Completion section.*

Getting Started as a Group Facilitator

Before the group training:

- Prepare an agenda for the training.
- Print a copy of each case study to be discussed, a post-test, and a curriculum evaluation form for each participant.
- Identify and reserve a centrally located room that is suitable for the group size and for computer projection. An ideal room arrangement is several tables that accommodate up to eight participants. This will enhance case study discussions.

- Rent or locate a computer for projection and a projection screen.
- Rehearse your presentation, preferably in the training room using the equipment to be used during the actual presentation.
- Gather other supplies, such as blank paper, pens, name tags, flip chart, and markers.

On the day of the training:

- Greet the participants as they arrive at the training site. Use name tags.
- Ask the participants to briefly introduce themselves.
- Tell participants that the training is based on the *Research Ethics Training Curriculum* developed by FHI to provide basic training in research ethics. It is targeted to researchers and members of Research Ethics Committees.
- Give an overview of the agenda and encourage active participation.
- Tell participants that a certificate of completion will be given to those successfully completing the training (the certificate may be issued by FHI or a local institution).
- Begin the curriculum presentation and follow the agenda.
- Facilitate active participation throughout the training, including general and specific comments and questions.
- Take refreshment breaks. A group lunch is helpful.
- Complete the curriculum presentation.
- Administer the post-test.
- Ask participants to complete the curriculum evaluation form.

Facilitator Tools

Below are the presentation materials for group training. The files are in Adobe PDF format and can be viewed and printed with Adobe Reader. (Users with Adobe Acrobat--a commercial program--will provide additional options for working with these PDF files. Should you need options other than printing and viewing, refer to the Adobe Web site for pricing and information on these additional options.)

Click on the icon(s) or link(s) below to open the presentation materials.

Color Slides for Online Presentation (78 screens)

This PDF file contains color slides for projection from a computer. The PDF format can be used like a slide show. For optimal viewing, we recommend that you save this file to your computer before running the slide show. Click on the icon above to open the file, then save the file to your computer by using the disk icon on the navigation bar. For presentation, open Adobe Acrobat Reader from your computer, then open the *Online Presentation* with Adobe Reader. Once the file is open, go to View and select Full Screen. Use the left and right arrow keys on the keyboard to move forward or backward through the presentation. Press the Escape key to go back to normal view.

Case Studies

This PDF contains case studies relating to the curriculum. Print copies of the cases you will discuss and distribute to each participant before each discussion.

Post-Test and Curriculum Evaluation Form

This PDF contains the post-test and curriculum evaluation form. Print copies of these materials and distribute to each participant at the end of the presentation.

The answers to the post-test and a blank *Certificate of Completion* are available exclusively to Group Training Facilitators. The post-test document is a password-protected PDF one. If you are a Facilitator and need access to these document, please e-mail ethics@fhi.org .

Important Note: We regret to inform self-study learners that they may not send in post-tests, evaluation forms or request *Certificates of Completion* directly from us. They have to complete and receive them online exclusively.

Overview

I. The Principles of Research Ethics

II. The Development of Contemporary Research Ethics

III. Informed Consent

IV. Responsibilities of Research Ethics Committees

V. Responsibilities of Sponsors and Researchers

VI. Community Participation in the Research Process

I. Principles of Research Ethics

Learning Objective:

- **Apply the three fundamental principles of research ethics in the development, review, and conduct of research involving human participants**

Dmitriy Margolin/Acclaim Images

Fundamental Principles of Human Research Ethics

- Respect for persons
- Beneficence
- Justice

Nash Herndon/FHI

The Meaning of Respect

Eva Canoutas/FHI

Respect for Persons (and Community)

- Autonomy, self-determination
- Capacity to decide, make choices
- The dignity of people and the individual
- Respect for the community and local culture

The Meaning of Beneficence

Barbara Barnett/FHI

Beneficence

- Physical, mental, and social well-being
- Risks reduced to a minimum, non-maleficence
- Protection of the participant is the primary responsibility of the researcher
- Benefits for the communities where the research is conducted

The Meaning of Justice

Tita Oronoz/FHI

Justice

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

Vulnerable Research Participants

Tita Oronoz/FHI

Vulnerable Research Participants
(continued)

- Pregnant women, children, prisoners
- Mentally ill
- Those with limited education
- The poor
- Those with difficult access to health services
- Women in some circumstances
- Sex workers

Summary—Principles of Research Ethics

- **All codes and regulations advocate three fundamental principles**
  - respect for persons
  - beneficence
  - justice
- **These principles apply not only to the person, but also to the community at large**
- **Vulnerable research participants require special protections**

Case Study 1—Principles of Research Ethics

1. Is the use of placebo permissible?
2. Is the design appropriate to demonstrate efficacy?
3. Should treatment for malaria cases be provided?
4. Should information on malaria prevention be provided?
5. Is local REC review and approval necessary?

II. The Development of Contemporary Research Ethics

Learning Objective:

- **Review and discuss the main national and international guidelines and regulations that guide the development and review of research studies**

Dmitriy Margolin/Acclaim Images

The Development of Contemporary Research Ethics

- **Guidelines, codes, and regulations developed to guide research involving human participants**

Eva Canoutas/FHI

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

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

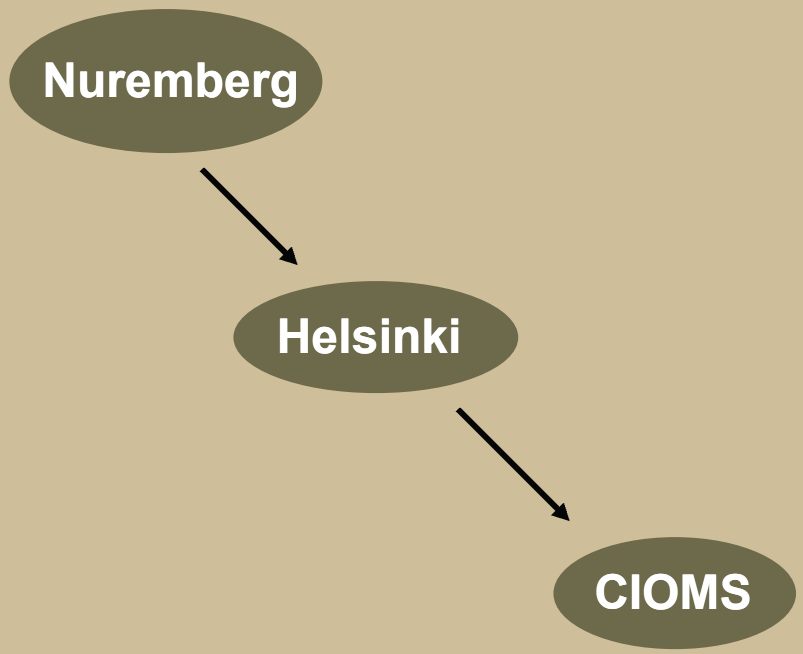
Bill Finger/FHI

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
- Role of ethics committees
- Community participation

International Conference on Harmonization (ICH)

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

Eva Canoutas/FHI

Other Reports and Guidelines

- National Bioethics Advisory Committee (NBAC)—Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries
- Nuffield Council on Bioethics—The Ethics of Research Related to Healthcare in Developing Countries
- HIV Prevention Trials Network—Ethics Guidance for Research

National Regulations

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

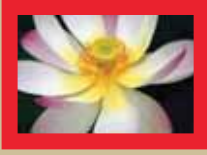
Summary—From Fundamental Ethical Principles to Local Guidelines

III. Informed Consent

Learning Objectives:

- **Recognize informed consent as a process**
- **List and explain the essential elements of informed consent**
- **Select the essential information that should be included in the informed consent process and when, how, and by whom it should be presented**
- **Develop an informed consent process that is culturally appropriate and understandable**

Dmitriy Margolin/Acclaim Images

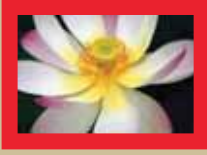


What Is Informed Consent?

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**

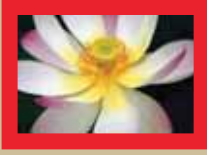
Source: CIOMS International Ethical Guidelines



Informed Consent as a Process

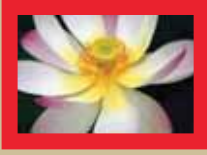
Informed consent is a communication process:

- Between the researcher and the participant
- Starts before the research is initiated
- Continues throughout the duration of the study



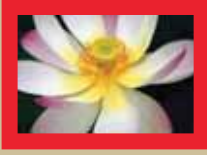
Informed Consent (before study initiation)

- Knowledge of the local culture and resources available
- Community participation
- Identification of risks and benefits, before and after the study
- Pilot testing
- Knowledge of the local REC requirements



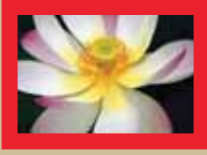
Informed Consent (study initiation)

- Information is presented
- Participant decides
- Who presents the information is important
- Support materials are helpful
- Understanding is assessed



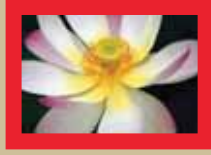
Informed Consent (during the study)

- Reinforce key points
- Communicate new information
- Address rumors



Information in Informed Consent

- Necessary versus excessive information
- Long forms versus short forms
- Common Rule and CIOMS Guidelines are valuable resources
- Not only what, but how, when, and by whom
- Participant understanding assessment necessary



Development of Informed Consent Materials

- Use local language
- Write for appropriate reading level
- Illustrate with appropriate concepts and images
- Perform a translation and back-translation
- Pilot test

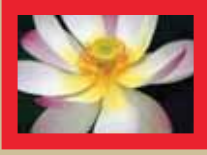
Community Representation and the Informed Consent Process

- Culturally appropriate guidance
- Community and participants' perspectives
- Possible vigilance of the process

Essential Elements of Informed Consent

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

Apophia Karanja/FHI



Description of the Research

- Research study
- Objectives of the study, duration
- Expected responsibilities
- Procedures involved, use of placebo
- Sponsor and responsible REC

Description of Risks

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

David Borasky/FHI

Description of Benefits

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

Eva Canoutas/FHI

Available Alternatives

- Alternative procedures or treatment
- Advantages and disadvantages
- Availability

S.J. Staniski

Confidentiality

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

Elizabeth Robinson/FHI

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

Elizabeth Robinson/FHI

Voluntary Participation

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

S.J. Staniski

Documentation of Informed Consent

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

Tita Oronoz/FHI

Waiver of Informed Consent

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

Summary—Informed Consent

- Ethical, not just legal requirement
- Documentation needed
- Comprehensibility essential, use support materials, pilot test
- Culturally appropriate
- Free of coercion

Case Study 2—Informed Consent

In this case, the REC should:

1. Recommend that the study be terminated.
2. Retrain the site investigator and the study staff in the informed consent process.
3. Rely on the site investigator's knowledge of the study population.
4. No action. Signed consent forms for each participant are on file.

IV. Responsibilities of Research Ethics Committees

Learning Objectives:

- Describe the role, composition, and function of Research Ethics Committees
- Comply with the requirements of the Research Ethics Committee in the development and conduct of a research study

Dmitriy Margolin/Acclaim Images

Research Ethics Committees

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

Eva Canoutas/FHI

Establishment of the REC

- **Defined through standard operating procedures**
  - authority under which the committee is established
  - criteria for selecting members
  - processes followed by the REC
- **Must work effectively with research staff**
- **Requires adequate resources**

Research Ethics Committee Members

- Members trained in research ethics
- Multidisciplinary
- Diverse in cultural and gender background
- Capable of assessing the relationship between the research and the community where it will be conducted
- Members willing to volunteer

Research 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

- Benefits to community?
- Consultation with community?

Research Ethics Committees: Criteria for Review and Approval (continued)

Care and Protection of Research Participants

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

Informed Consent

- Complete information?
- Written documentation?

Confidentiality Issues

- Adequate protection?
- Risk of breach?

Research Ethics Committees: Additional Responsibilities

The role of the REC extends beyond the initial review and approval of a research study, including:

- **Conducting regular review of ongoing research**
- **Reviewing all modifications and amendments to approved research**
- **Monitoring active research studies for compliance**
- **Investigating problems that could impact the safety of participants**

Data and Safety Monitoring Boards (DSMB)

- Independent
- Technical experts
- Review safety data and compare study arms
- Authority to “break the blind”
- Rules for stopping the research
- Complementary to the mission of the REC

Protecting Research Participants: Other Stakeholders

- Sponsor or monitor
- Regulatory agencies
- Institutional regulatory and compliance offices
- Public interest groups

Bill Finger/FHI

Summary—Research Ethics Committees

- Cornerstone for the protection of research participants
- Complemented by Scientific Review Committees, DSMBs, and other oversight mechanisms
- Unofficial oversight can also influence the implementation of a study

Case Study 3—REC Considerations

1. Is the study methodology appropriate?
2. Should the study be reviewed and approved phase by phase?
3. Are the protections for participants sufficient?
4. Should Phase Ib be eliminated?

V. Responsibilities of Sponsors and Researchers

Learning Objective:

- **Comply with the responsibilities of sponsors and researchers in the development and conduct of research studies**

Dmitriy Margolin/Acclaim Images

Sponsor's Responsibilities

- Select qualified researchers
- Provide necessary support
- Require appropriate ethical review
- Promote research integrity

Sponsor's Responsibilities in International Research

- Comply with the local ethical, regulatory, and legal requirements
- Ensure the local relevance of the research
- Assist in capacity building
- Post-trial responsibilities

Researcher's Responsibilities

Protection of research participants

- Scientific correctness
- Appropriate informed consent
- Confidentiality protection

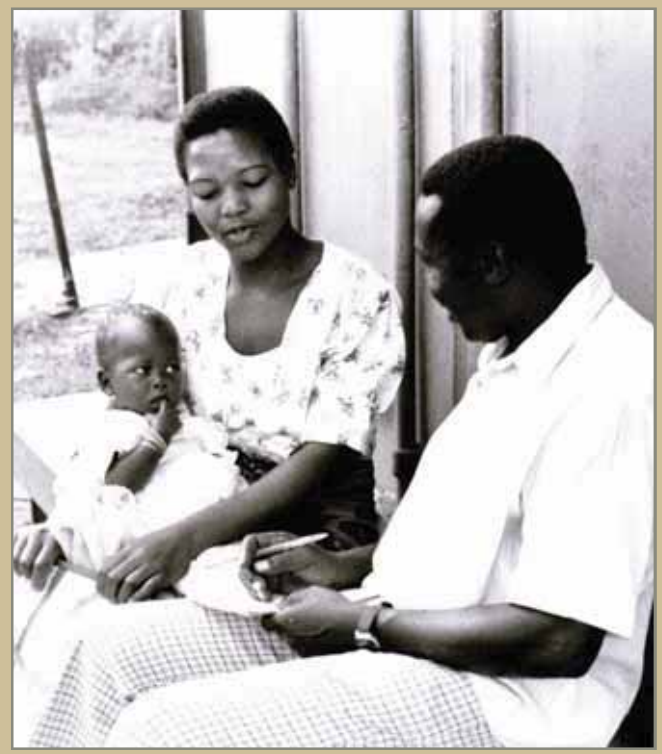
Nash Herndon/FHI

Researcher's Responsibilities (continued)

- **Conduct the research according to the protocol**
- **Conduct the research with integrity**
- **Compliance with REC 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



Rebecca Kohler/FHI

Summary—Responsibilities of Sponsors and Researchers

Shared responsibilities in research process

- Protection of research participants
- Well-designed research
- Adequately reviewed
- Ethically conducted
- Properly disseminated

VI. Community Participation in the Research Process

Learning Objectives:

- Define a community
- Explain how to involve community representatives in the research process
- Identify possible roles of a community representative

Dmitriy Margolin/Acclaim Images

Activity

- **What is a community?**
- **What kind of community is shown in this slide?**
- **Why is this a community?**

Sara A. Holtz/Peace Corps

Characteristics of a Community

A group linked by:

- Location
- Common perspectives
- Joint action

S.J. Staniski

Special Research Communities

- By disease
- By occupation
- By population
- By location

Mario Chen/FHI

Activity

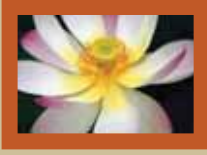
Is it important to have community representatives participate in the research process?

Partners in Community-Based Research: A Model

Community

REC/IRB

Research staff



Why Have Community Participation?

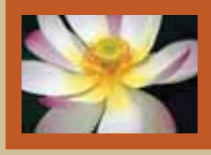
- To build a bridge between the community and the research and researchers
- To voice local questions and concerns
- To represent the interests of participants

Community Participation in the Research Process

- **Before the study**
  - inform the community
- **During the study**
  - follow study progress
- **After the study**
  - share the research findings

Shyam Thapa/FHI

Responsibilities of Community Representatives



- Ensure that research is responsive to community needs and expectations
- Advocate for the well-being of research participants
- Ensure appropriate informed consent
- Promote access to research benefits

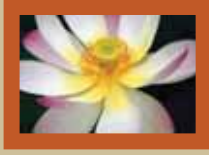
Primary Responsibilities of RECs and Community Representative Groups

- RECs are the only group responsible for the review and approval of research protocols
- Community representative groups advise researchers in the development and conduct of the research study
- So far, only RECs are required by regulations

Ethics Committees	Community Representatives
Protect research participants by applying the principles of research ethics and any relevant guidelines and regulations	Represent the interests of research participants
Conduct initial review and approval of the protocol and any future changes	Advise the researchers on the protocol, participate in community education and outreach activities
Review the informed consent and other materials intended for research participants	Provide input into the informed consent process; review support materials for linguistic and cultural relevance
Conduct continuing review and monitoring of ongoing studies	Alert the researchers to problems arising during the study
Document and archive study documents	Advise the researchers on how to best disseminate research results

Summary—Community Participation in the Research Process

- Community definition: individuals share common characteristics
- Community participation: individuals promote and enhance the interests of their community
- Community representation: individuals assume many roles and responsibilities on behalf of their community



Case Study 4— Community Participation

1. Can this injecting-drug user population (community) be included in this study? Why or why not?
2. What measures can the research staff take to ensure that informed consent is given freely by all participants?
3. If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?

Conclusion

- Additional materials
- Post-test and certification
- Contact information:

Office of International Research Ethics
Family Health International
P.O. Box 13950
Research Triangle Park, NC 27709 USA
E-mail: ethics@fhi.org
Web: www.fhi.org

Overview

This curriculum consists of six main sections, each focusing on a core area related to research ethics. In addition, it provides case studies, evaluations, references, and copies of key documents. The core areas are:

I. The Principles of Research Ethics
II. The Development of Contemporary Research Ethics
III. Informed Consent
IV. Responsibilities of Research Ethics Committees
V. Responsibilities of Sponsors and Researchers
VI. Community Participation in the Research Process

The *Research Ethics Training Curriculum* (RETC) uses the image of a **lotus flower to represent purity and perfection.** Ethical considerations that aim for the ideal of a pure and perfect research design should be the foundation on which all research studies are developed and implemented.

I. Principles of Research Ethics

The learning objective for the *Principles of Research Ethics* section is to:

- Apply the three fundamental principles of research ethics in the development, review, and conduct of research involving human participants.

Learner/Facilitator 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.

Fundamental Principles of Human Research Ethics

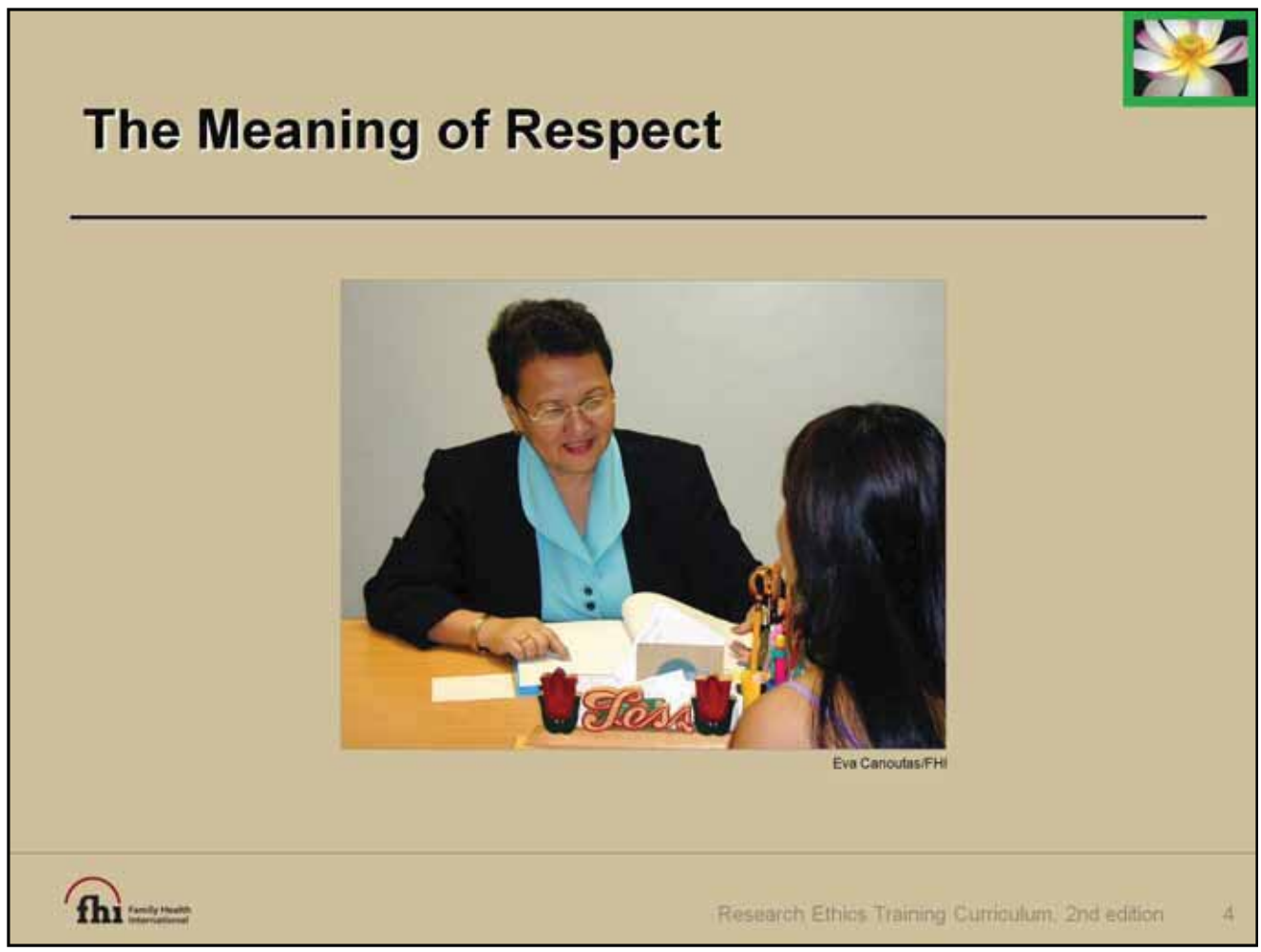
Human research ethics rest on **three fundamental principles** that are considered the foundation of all regulations or guidelines governing research ethics. These principles are:

- Respect for persons
- Beneficence
- Justice

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

Researchers, institutions, and Research Ethics Committees (RECs) have the responsibility to assure that these principles are followed whenever research on humans is conducted. However, the principles by themselves do not protect the research participants; it is necessary to create systems or mechanisms, including norms and procedures, based on these principles that would directly protect participants.

Although these principles are universal, the availability of the resources needed to maintain these principles is not universal. Such limitations are particularly noticeable in some developing countries where procedures may not be optimal for the ethical vigilance of research studies. Particularly limited are the resources available to local RECs to correctly review, approve, and monitor research studies. Regardless of limitations, these principles must guide the behavior of all individuals involved in sponsoring, planning, reviewing, implementing, and monitoring human research.



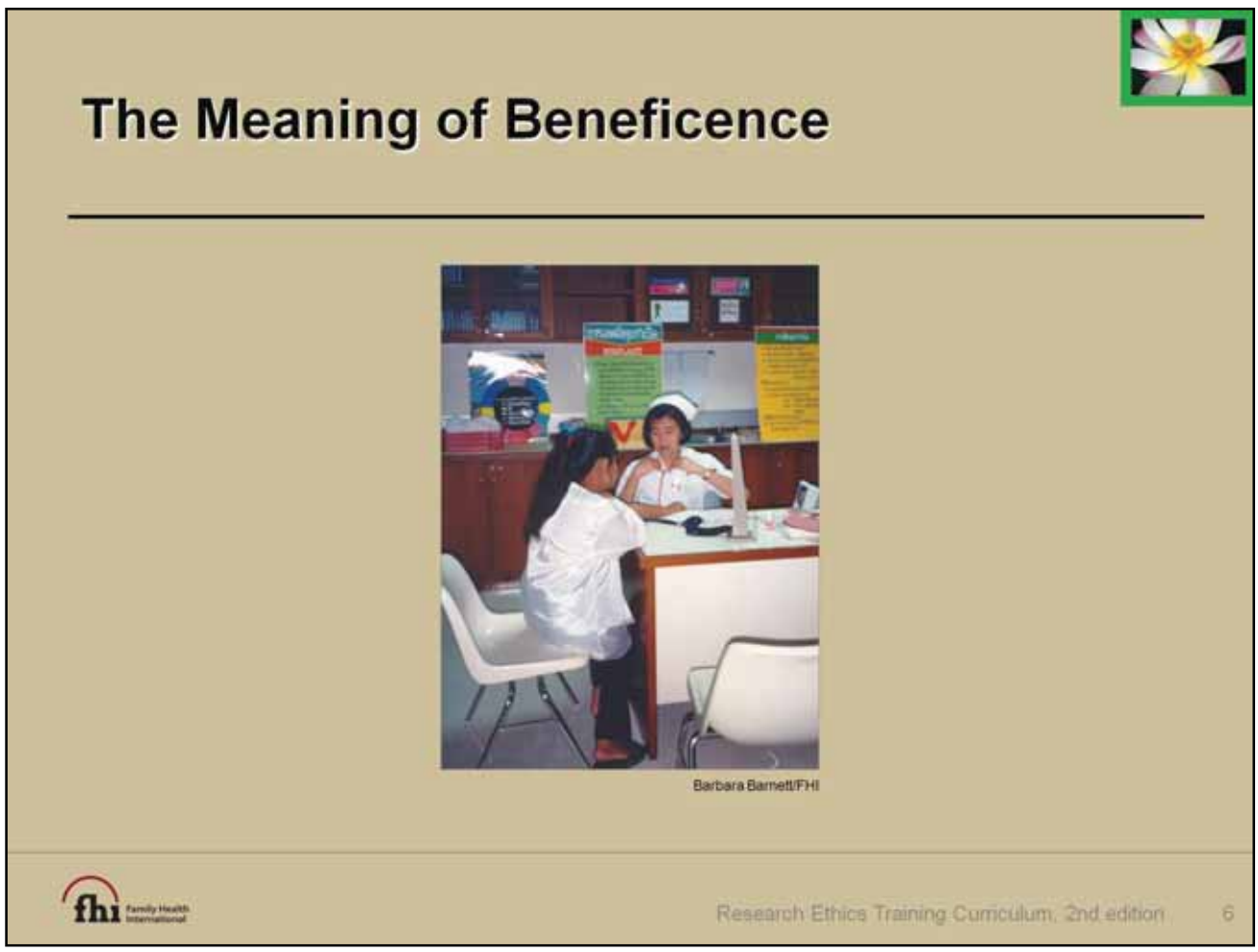
The Meaning of Respect

Learner/Facilitator Note: At this point, the self-learner should attempt to list three examples of the meaning of respect. For group training, ask participants to call out answers.

Respect for Persons (and Community)

Respect for persons recognizes the right and capacity of all individuals to make their own choices and decisions. It refers to respect for the autonomy and self-determination of all human beings, their freedom, and their capacity to decide. In some cultures, respect for the dignity of the person is particularly important. Respect for autonomy does not mean only providing information and respecting individual decisions; it implies that researchers are obligated to create the conditions in which people can make free and informed decisions. The informed consent process in a research study should be designed to empower a person to decide whether or not to participate in the study. Special consideration must be given to persons who may have a diminished capacity to make their own choices due to physical, mental, social, or economic reasons.

Originally, the concept of respect referred only to the person. Today, the principle of respect for persons also includes respect for the person's culture and beliefs and for the community to which the potential participant belongs. It is necessary to identify and respect the particular decision-making process of each community.



The Meaning of Beneficence

Learner/Facilitator Note: At this point, the self-learner should attempt to list three examples of the meaning of beneficence. For group training, ask participants to call out answers.

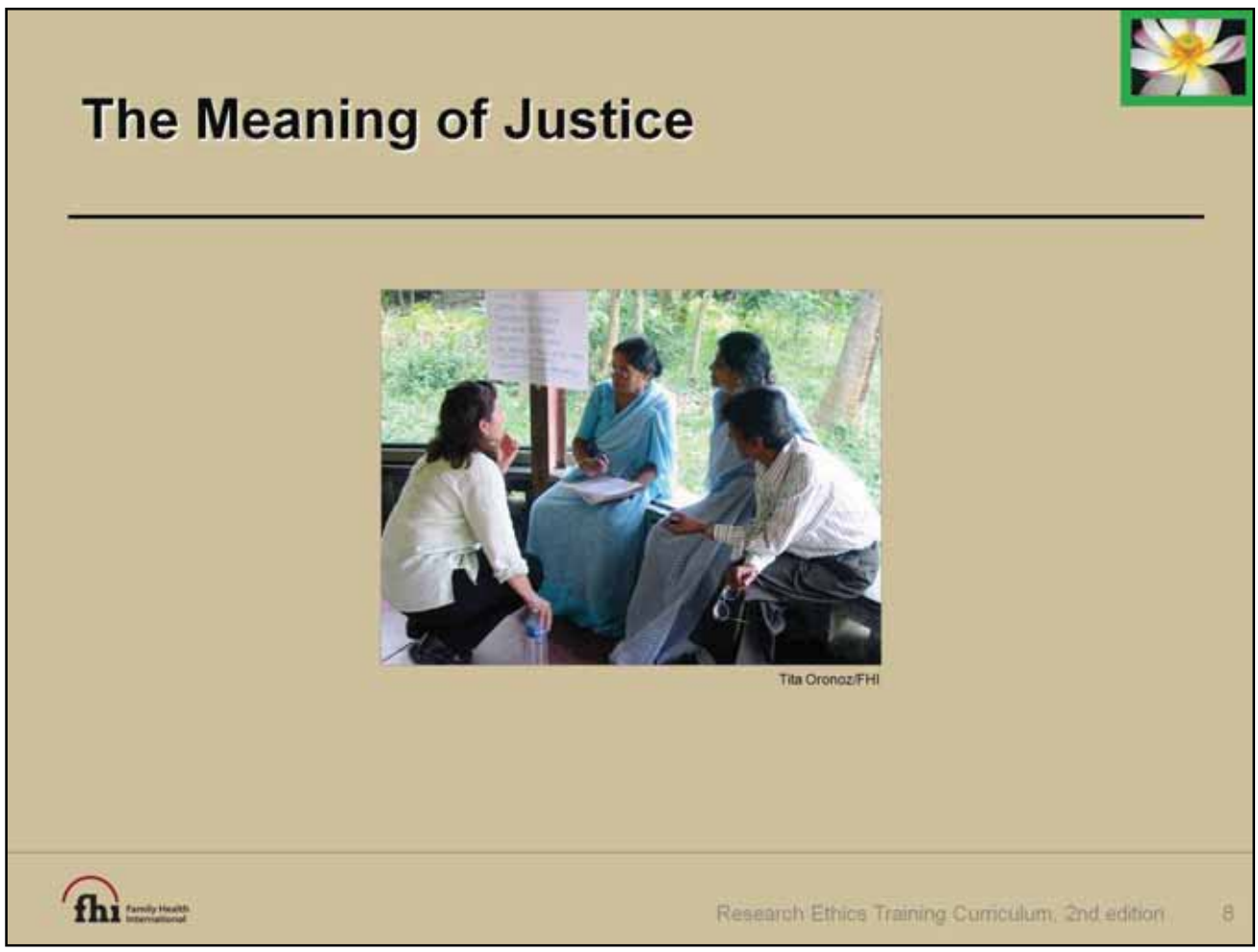
Beneficence

The principle of beneficence holds the researcher responsible for the participant's physical, mental, and social well-being throughout participation in the study. Benefits to the participant must be weighed against potential risks that the person might have by participating. The risk/benefit analysis is a key process in the development (by researchers), and review and approval (by RECs) of a research study.

The medical expression "do no harm" applies to the principle of beneficence. The term "non-maleficence" has similar meaning and was once considered to be a separate principle, independent of beneficence. In some documents, non-maleficence is still considered an independent fourth principle of research ethics.

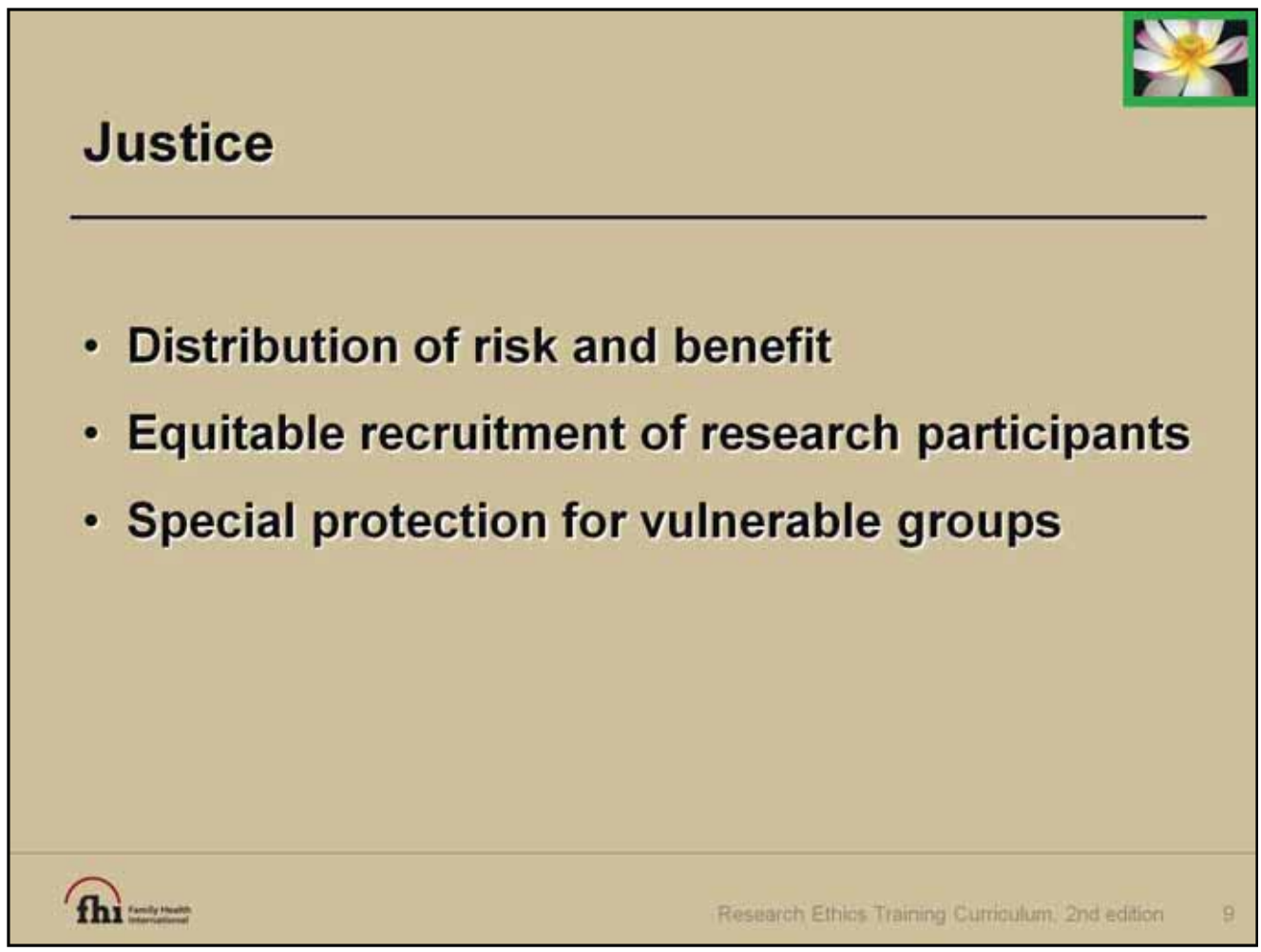
The protection of the well-being of the research participant is the primary responsibility of the researcher. Protecting the participant is more important than the pursuit of new knowledge, the benefit to science that may result from the research, and personal or professional research interests.

At present, special consideration is given to possible benefits not only to the research participants, but also to the communities where the research will be conducted. In general, a research study should only be justified if its conduct and results will be of benefit to the community. How or whether the community will benefit must be very clear in a research protocol and be made known to the community.



The Meaning of Justice

Learner/Facilitator Note: At this point, the self-learner should attempt to list three examples of the meaning of justice. For group training, ask participants to call out answers.



Justice

The principle of justice forbids placing one group of people at risk solely for the benefit of another. **The researchers and sponsors have the obligation to distribute the risk and benefits in an equitable manner for both potential participants and communities.**

The Belmont Report states that "in the early 20th century, 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." It also states that justice demands that "research should not unduly involve persons unlikely to be among the beneficiaries of subsequent applications of the research." The recent UNESCO Universal Declaration on Bioethics and Human Rights says: "The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably." The principle of justice would not permit using vulnerable groups as research participants for the exclusive benefit of more privileged groups.

Low-resource communities should not be used for the benefit of more privileged communities, and possible benefits to the community where the research would be conducted should be addressed in the study protocol and its review by an REC.

Access to health interventions scientifically proven to be safe and effective should be made available to both research and non-research participants. Development of new interventions and their future use is the main goal of biomedical research. However, the provision of new interventions and high-quality services is not the direct responsibility of researchers and sponsors; it is mainly the responsibility of policy-makers, public health officials, and society at large. All stakeholders should give due consideration to this issue and identify possible areas of collaboration when the research is being developed.

Learner/Facilitator Note: The UNESCO Universal Declaration on Bioethics and Human Rights is included in the *Additional Resources* section under *Useful Internet Sites*.

Vulnerable Research Participants

Learner/Facilitator Note: At this point, the self-learner should attempt to list three examples of vulnerable research participants. For group training, ask participants to call out answers.

Vulnerable Research Participants (continued)

The three research ethics principles, and the guidelines derived from them, call for special protection of vulnerable research participants. The Council for International Organizations of Medical Sciences (CIOMS) defines vulnerability as "substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group."

The need to provide additional protections to some special groups, such as pregnant women or fetuses, neonates, children, or prisoners, is considered in many regulations. However, recent attention has been given to participants who may be vulnerable due to their cultural, social, or economic characteristics. Examples are persons with limited education, low income, or limited access to health care services. Persons with these characteristics may decide to participate in research studies because they believe it is the only opportunity of obtaining needed medical care; wrongly perceive that they will obtain free, effective treatments; or are tempted to take risks they would not take otherwise. In some cultures, women must defer to men in the decision-making process. Gender bias is present in most cultures, and both women and men may be placed in vulnerable research situations.

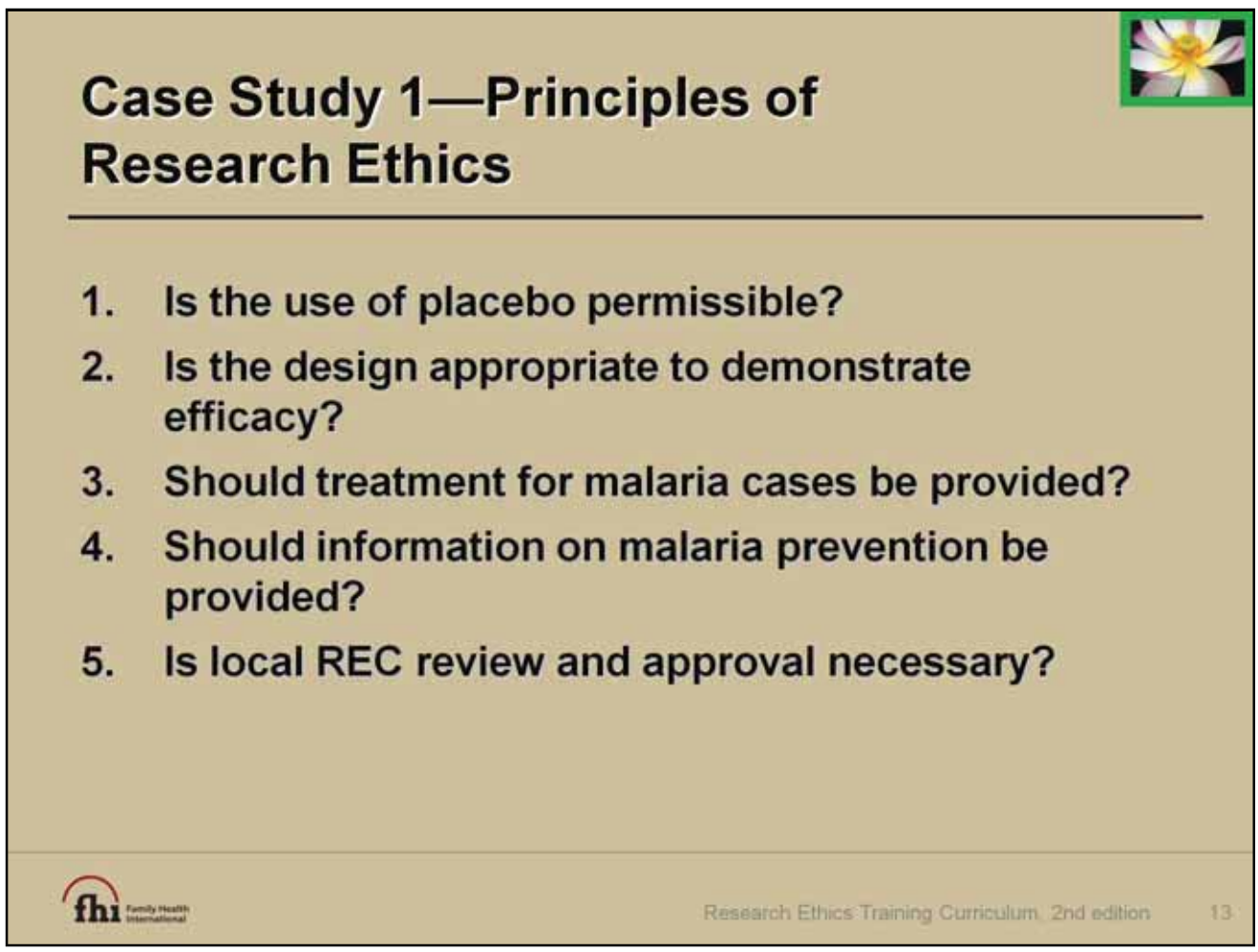
These conditions may compromise a person's ability to refuse participation. Such conditions are more common in developing countries, making entire populations vulnerable. The need to provide sufficient protections must be carefully considered by researchers and RECs. The Universal Declaration on Bioethics and Human Rights says: "Unethical scientific and technological conduct has had a particular impact on indigenous and local communities."

The informed consent process is designed to empower the potential participant to make a voluntary informed decision, free of coercion, on whether to participate or not in a research study. RECs have the responsibility to assure that the informed consent process is appropriate for vulnerable individuals or groups.

Summary—Principles of Research Ethics

While there are many different guidelines governing research with human participants, each demands from the researcher respect for persons, beneficence, and justice. Researchers work within the framework of a particular society, and the norms of that society must be followed in harmony with the rules of science and research. The principles of research ethics apply not only to the person, but also to the communities where the research will be conducted. **Research with human participants is a privilege, not a right,** and is given to the researcher by the society.

However, merely following written regulations is insufficient. The research community must strive to meet, if not exceed, the spirit contained in these principles and guidelines. In doing so, it places the safety and well-being of the research participant before everything else.



Case Study 1—Principles of Research Ethics

Questions:

1. Is the use of placebo permissible?
2. Is the design appropriate to demonstrate efficacy?
3. Should treatment for malaria cases be provided?
4. Should information on malaria prevention be provided?
5. Is local REC review and approval necessary?

Learner/Facilitator Note: At this point, the self-learner should review the case study, included in the *Case_Studies* section. The facilitator should have made copies of this case study to hand out to each of the group training participants. The Facilitator should also have carefully reviewed the instructions in the *Case Studies* section.

II. The Development of Contemporary Research Ethics

The learning objective for the *Development of Contemporary Research Ethics* section is to:

- Review and discuss the main national and international guidelines and regulations that guide the development and review of research studies.

Learner/Facilitator Note: Key reference documents that are discussed in this section are included in the *Additional Resources* section, under *Basic Research Ethics Documents*.

The Development of Contemporary Research Ethics

Guidelines, codes, and regulations have been created in recent decades to guide the conduct of research involving human participants. The development of some of these documents was driven by historical events. Others were developed in response to the increasing globalization of research. And still others were created in an attempt to provide answers to new problems and challenges created by a dynamic research environment. Each reflects the principles of respect for persons, beneficence, and justice.

In this part of the curriculum, we will examine the chronological development of these documents, which have an important influence on the design and conduct of international research today.

The Nuremberg Code

At the end of World War II, the International Military Tribunal prosecuted Nazi war criminals, including physicians who performed experiments on concentration-camp prisoners. The tribunal's decision includes what is now called the Nuremberg Code, a 10-point statement guiding physicians in the conduct of research on human participants.

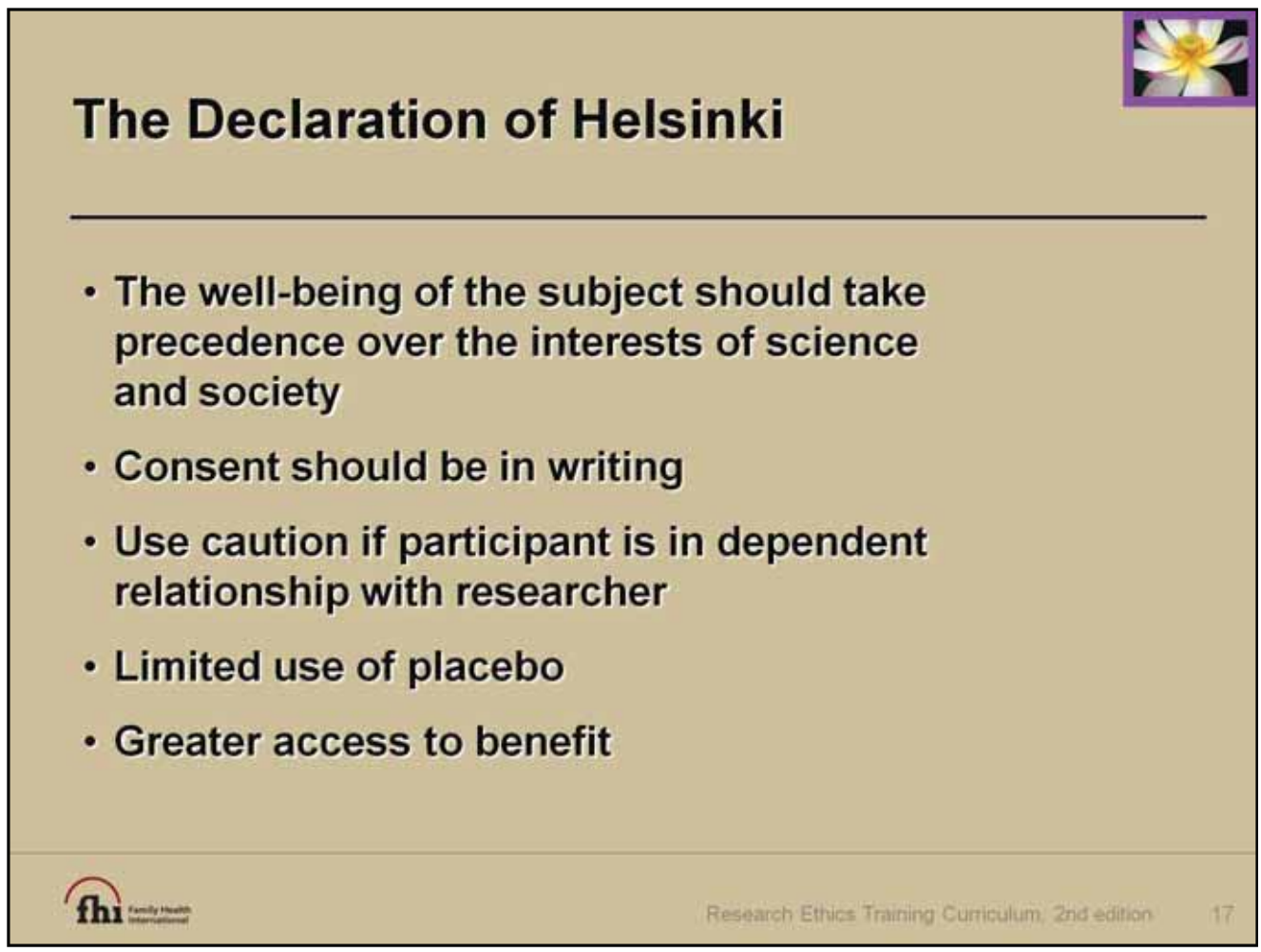
This document mandates conditions under which research can be ethically conducted. The first provision of the code requires that **"the voluntary informed consent of the human subject is absolutely essential."** The code provides other details implied by such a requirement:

- 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 is limited; it does not specifically address clinical research in patients with illnesses. Future documents would build on and expand the concepts in the Nuremberg Code.

Learner/Facilitator Note: The full text of the Nuremberg Code can be viewed on the Internet. The URL is included in the *Additional Resources* section under *Useful Internet Sites*.



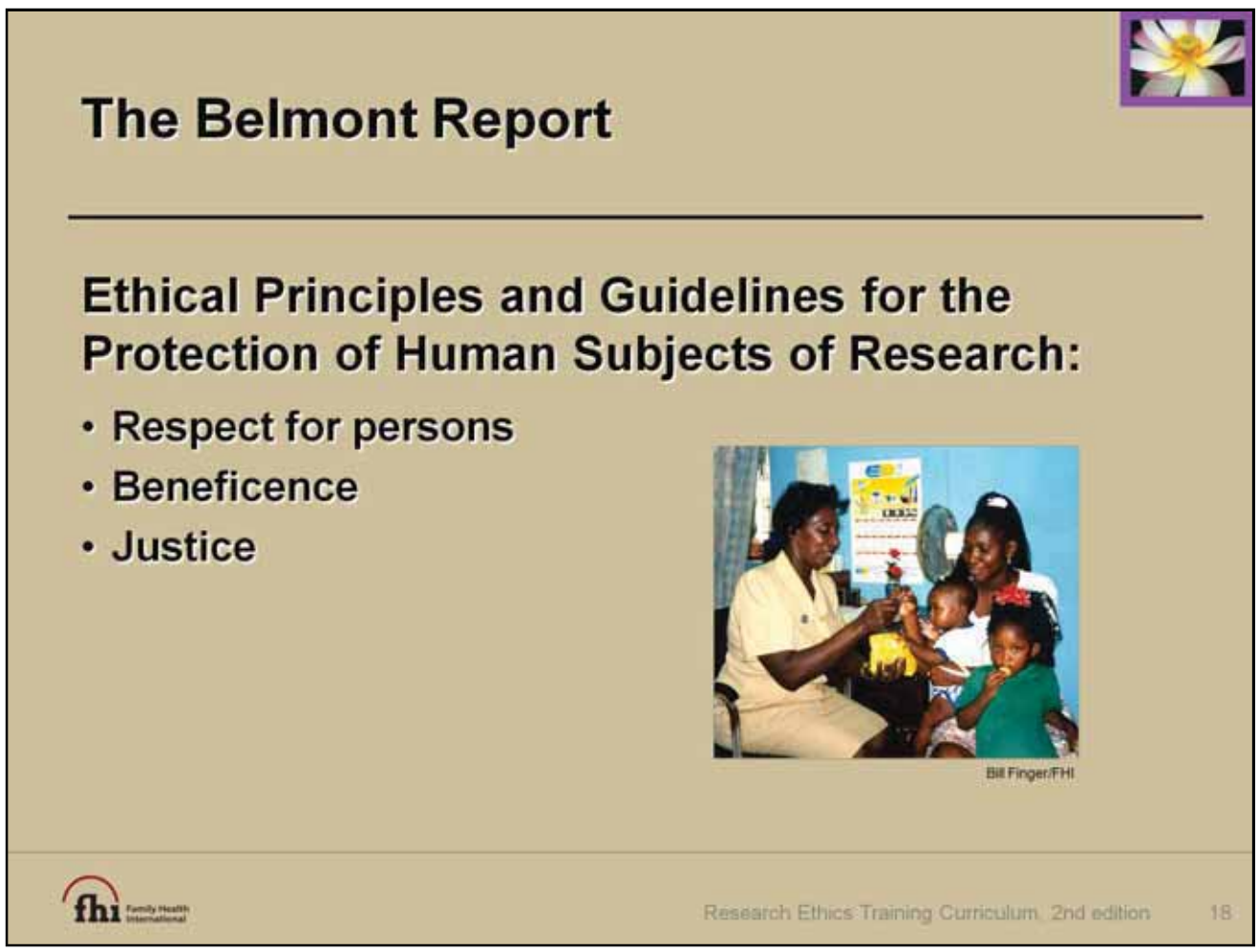
The Declaration of Helsinki

The World Medical Association (WMA)—inspired in part by the revelations of the Nuremberg trials—felt that there was a need to provide the global community of physicians with guidelines for conducting biomedical research involving human participants. The Declaration of Helsinki, which was first published in 1964, is considered by many to be the first world standard for biomedical research. 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 documentation of informed consent, extra protections for persons with diminished autonomy, and caution on the part of the physician-researcher who enrolls his own patients.

The most recent revision of the declaration in 2008 included two controversial paragraphs. Paragraph 32 requires that "the use of placebo, or no treatment, is acceptable only in studies where no current proven intervention exists" or where, for compelling and scientifically sound methodological reasons, the use of placebo is necessary and participants will not be subject to any serious risk. Paragraph 33 requires that "patients entered into the study are entitled to access to interventions identified as beneficial in the study or other appropriate care or benefits."

Due in part to these requirements in the declaration, the U.S. Food and Drug Administration (FDA) amended its regulations in October 2008, requiring that non-IND (investigational new drug) foreign clinical studies be conducted in accordance with Good Clinical Practices (GCP) instead of the Declaration of Helsinki. The FDA position was that the requirement for placebo use was inconsistent with current standards for clinical trial design as defined by U.S. law, and the access requirement "invokes issues of health care policy not directly related to FDA's mission."

Learner/Facilitator Note: The full text of the Declaration of Helsinki is included in the *Additional Resources* section under *Basic Research Ethics Documents*.



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. In this U.S.-government-sponsored study, more than 400 men with latent syphilis were followed for the natural course of the disease rather than given treatment. The study continued to deny treatment even after the discovery of penicillin in the 1940s. This study was all the more infamous because the participants were all poor African-Americans, a vulnerable and disadvantaged group in the southern United States at the time.

As a result, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974. 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 and is the basis for the U.S. federal regulations governing research.

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

Learner/Facilitator Note: The full text of the Belmont Report is included in the *Additional Resources* section under *Basic Research Ethics Documents*.

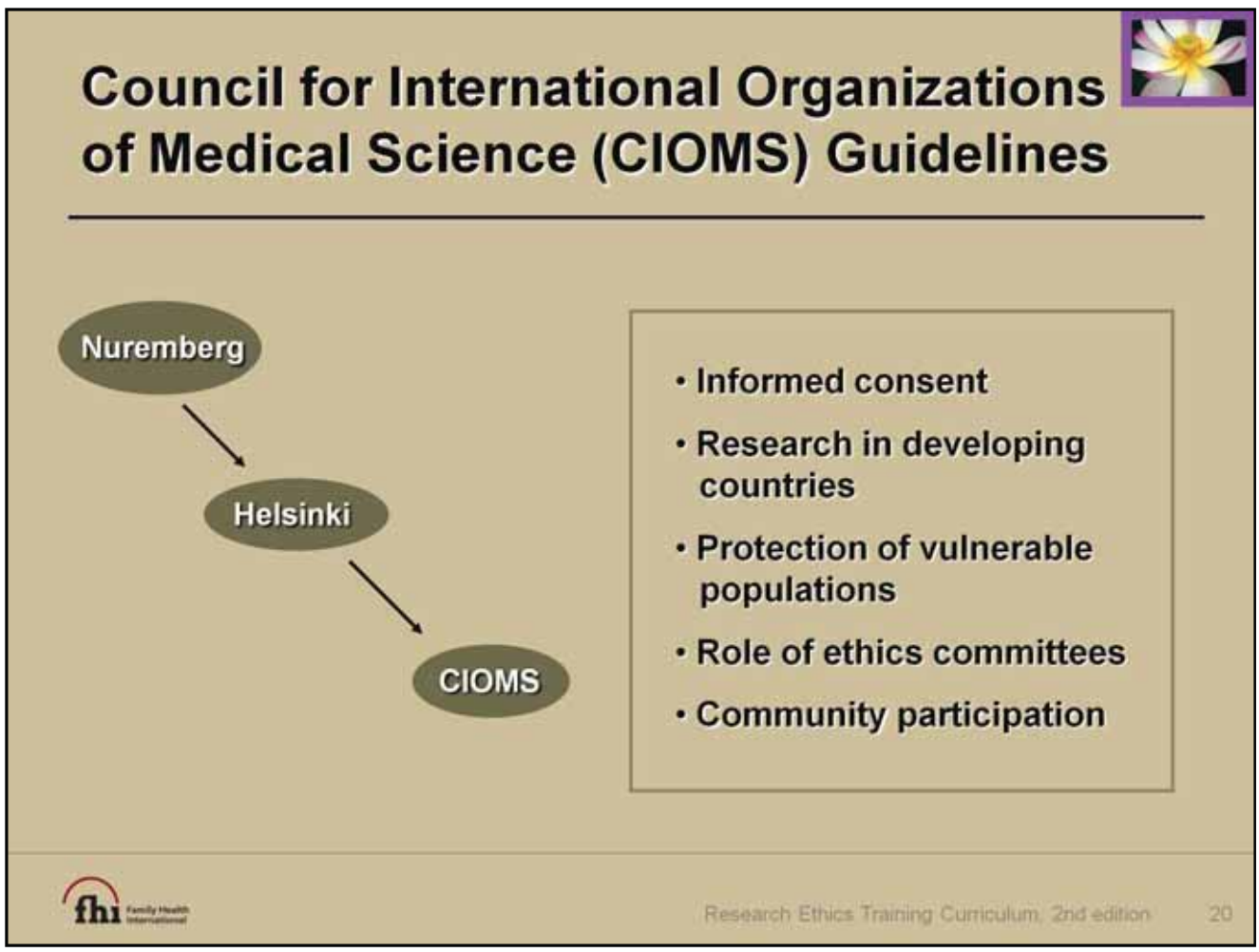
The U.S. Code of Federal Regulations (also called the Common Rule)

This code applies to nearly all research sponsored by the U.S. government, conducted nationally or internationally. 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 unofficial title, the Common Rule is designed to standardize the human participant protection system across U.S. federal agencies and departments. Institutions conducting research that is funded by the U.S. government must agree to abide by the Common Rule.

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/Facilitator Note: The full text of the Common Rule is included in the *Additional Resources* section under *Basic Research Ethics Documents*.



Council for International Organizations of Medical Science (CIOMS) Guidelines

CIOMS has been active in bioethics for many years. In 1982, CIOMS issued the *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects* "to indicate how the ethical principles ... set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries." The guidelines were revised in 1993 and 2002.

The current guidelines are based on the three principles of research ethics and consist of 21 guidelines, each followed by interpretive commentary. The CIOMS Guidelines are designed to be used in developing national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human participants. Topics include:

- Informed consent
- Research in developing countries
- Protection of vulnerable populations
- Role of ethics committees
- Community participation

Also included are the obligations of the sponsor, the researcher, and the host country. It is noted in the introduction to the guidelines that "the challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care." The CIOMS Guidelines take the position that research involving humans must not violate any universally applicable ethical standards, but acknowledge that, in certain aspects, the application of the ethical principles (e.g., in relation to individual autonomy and informed consent) needs to consider cultural values while respecting ethical standards. The CIOMS Guidelines are widely used as a reference.

Learner/Facilitator Note: The full text of the 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects is included in the *Additional Resources* section under *Basic Research Ethics Documents*.

International Conference on Harmonization (ICH)

In 1990, representatives of the regulatory agencies and industry associations of the United States, Japan, and Europe met and formed the International Conference on Harmonization (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 Guidelines for Good Clinical Practice (GCP). The GCP Guidelines are intended to provide standards for ethical and scientific quality for developing, conducting, and recording clinical trials. GCP is the standard for conducting clinical trials in the pharmaceutical industry.

The GCP Guidelines require review by an ethics committee and informed consent of participants. In addition, the guidelines detail the responsibilities of both the sponsor of the research and the researcher who conducts it.

As mentioned in the section on the Declaration of Helsinki, the FDA now requires that non-IND foreign studies be conducted in accordance with GCP, including review by an independent ethics committee (IEC).

In 2006, the World Health Organization (WHO) published the *Handbook for Good Clinical Research Practice* to aid researchers in the implementation of GCP standards in all types of human research.

Learner/Facilitator Note: The full text of ICH GCP Guidelines and the WHO *Handbook for Good Clinical Research Practice* may be viewed on the Internet. The URLs are included in the *Additional Resources* section under *Useful Internet Sites*.

Other Reports and Guidelines

The codes, regulations, and guidelines previously presented have been augmented by a number of independently developed reports and guidelines that focus on the ethical challenges of research in low-resource settings.

A 2001 report from the National Bioethics Advisory Committee (now disbanded) 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 development and implementation of the research. Additionally, the report states that the informed consent process must be culturally appropriate.

The U.K.-based Nuffield Council also reported on ethical issues in international research in its 2002 publication, *The Ethics of Research Related to Healthcare in Developing Countries*. The purpose of this report is to examine the ethical issues raised when research related to health care is conducted in developing countries and funded by sponsors from developed countries. The council's main recommendations focus on the inclusion and development of local partners in the research.

The 2003 guidance from the HIV Prevention Trials Network (HPTN) Ethics Working Group was developed for members of a defined research community—in this case, HIV prevention researchers. It states that the goal of the document is "to foster best efforts and best practices in the conduct of HPTN research by raising awareness of ethical considerations, engaging network members at all levels in dialogue about those considerations, and facilitating ethical decision-making at key points in the research process." This guidance emphasizes mutual accountability among peers and the thoughtful translation of ethical considerations into action.

Learner/Facilitator Note: The full text of these and other relevant reports may be viewed on the Internet. The URLs are included in the *Additional Resources* section under *Useful Internet Sites*.

National 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 or guidelines and the establishment of an infrastructure to supervise such research. **The rapid rise in the amount of research conducted in low-resource settings has further exposed the need for the creation of national regulations and for the appropriate support of its implementation.**

Many countries—such as Brazil, Canada, India, Mexico, Nepal, South Africa, Thailand, and Uganda— have national regulations on the conduct of human research. However, many countries still lack or are developing formal 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.

The U.S. Office for Human Research Protections maintains the International Compilation of Human Subject Research Protections, which it describes as "a listing of the laws, regulations, and guidelines that govern human subjects research in many countries around the world." As of 2010, the listing included information from 96 countries." The reference in the Useful Internet Sites need to say: http://www.hhs.gov/ohrp/international/HSPCompilation.pdf

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

The International Compilation of Human Subject Research Protections may be viewed on the Internet. The URL is included in the *Additional Resources* section under *Useful Internet Sites*, U.S. Department of Health and Human Services.

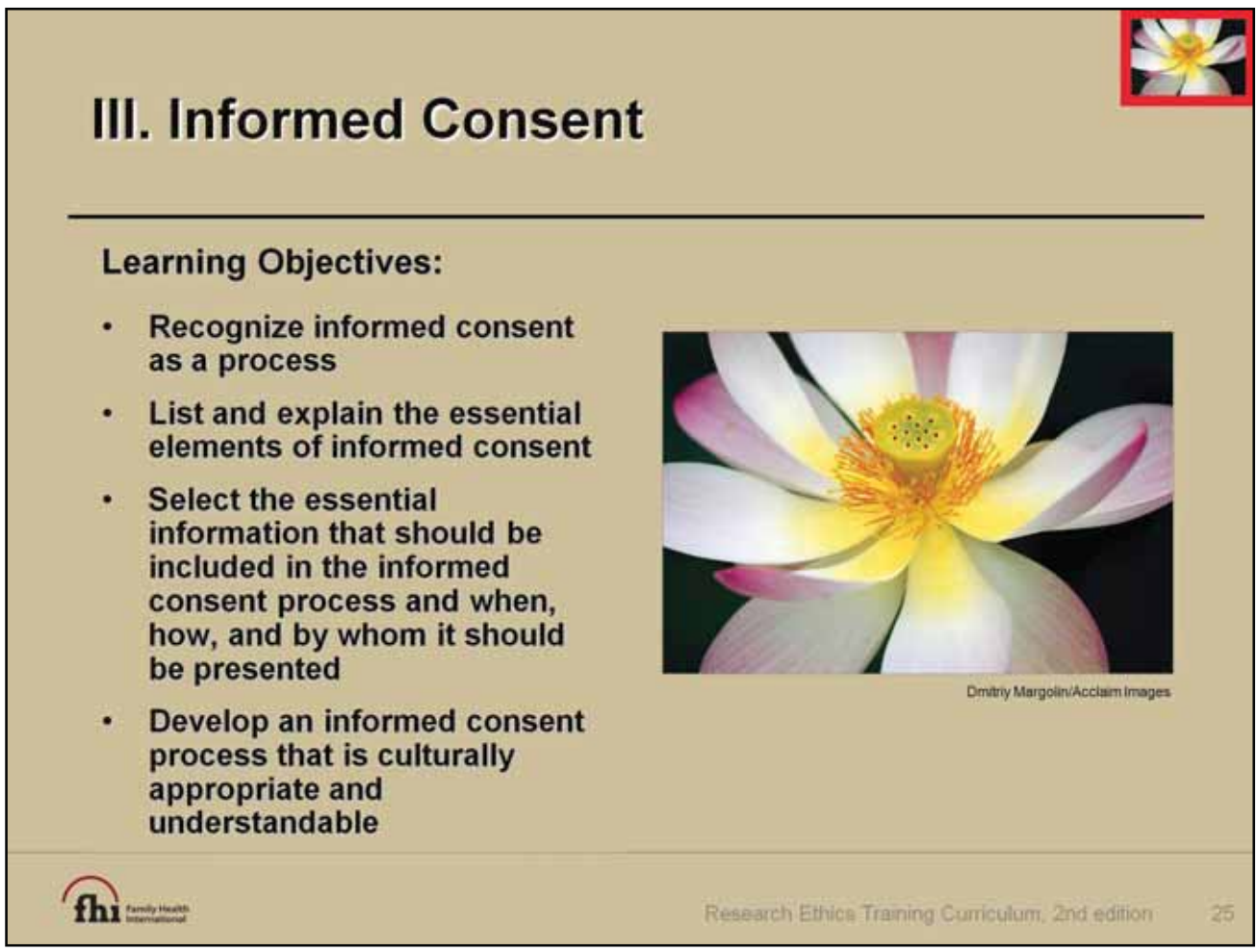
Summary—From Fundamental Ethical Principles to Local Guidelines

The three 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 guidelines.

Eventually, **these regulations and guidelines need to be adapted or transformed into institutional standard operating procedures** (SOPs) to be used at the local level to guide the planning, review, approval, and conduct of human research.

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

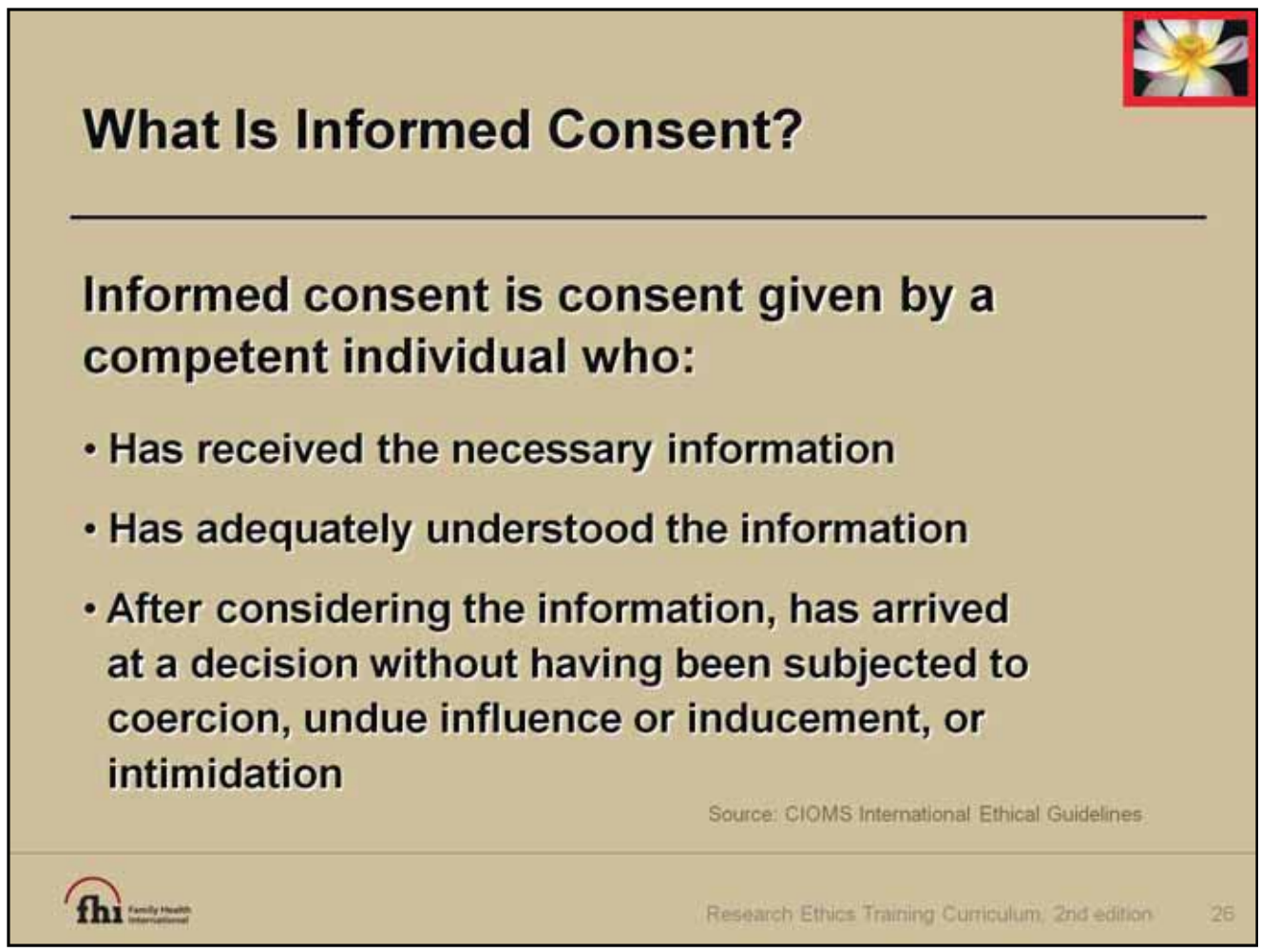
However, the majority of these documents are living documents, meaning that they are constantly evolving to address the new challenges faced by those who do research. Since their first publications, The Declaration of Helsinki and the CIOMS Guidelines have been revised many times.



III. Informed Consent

The learning objectives for the *Informed Consent* section are to:

- Recognize informed consent as a process
- List and explain the essential elements of informed consent
- Select the essential information that should be included in the informed consent process and when, how, and by whom it should be presented
- Develop an informed consent process that is culturally appropriate and understandable



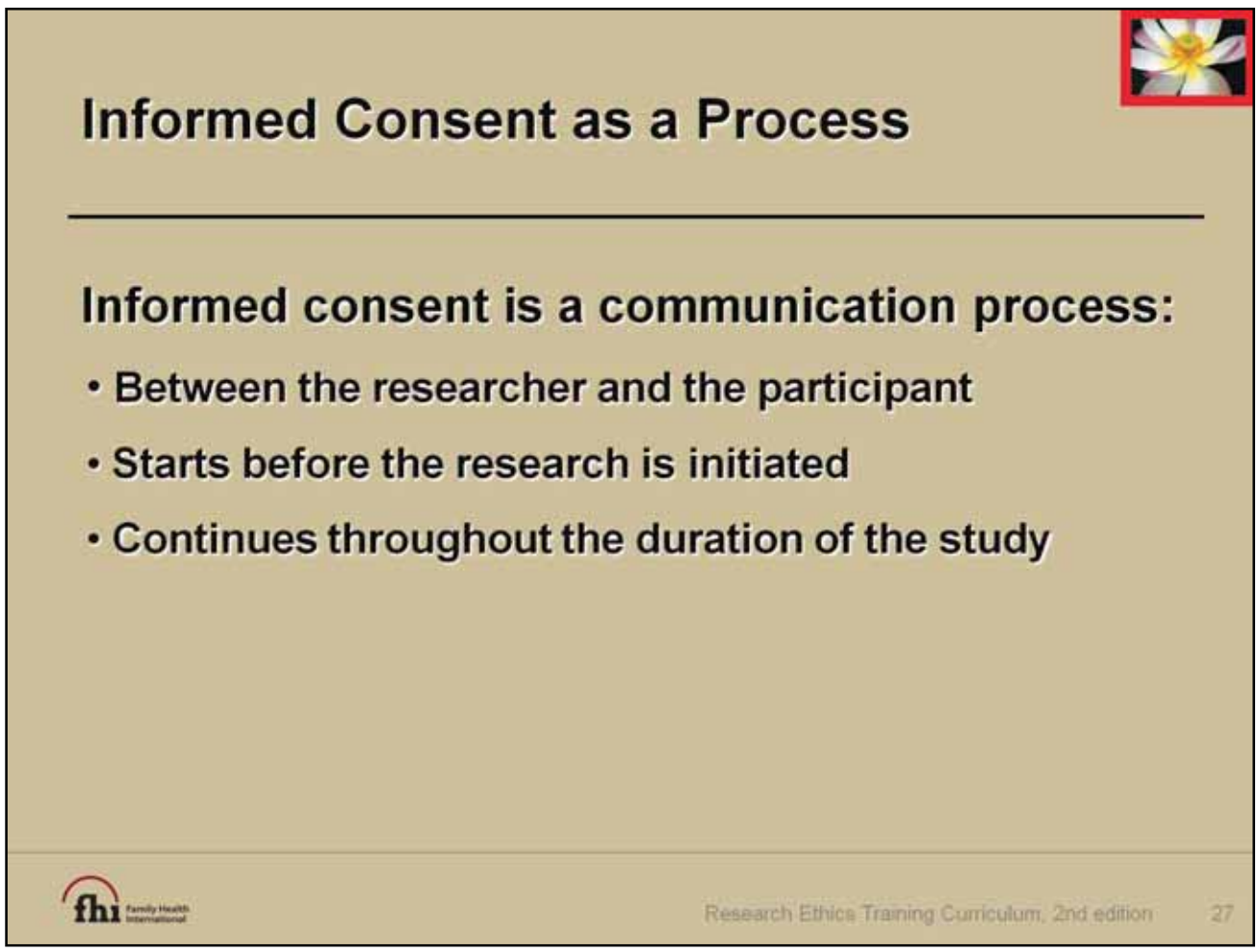
What Is Informed Consent?

Informed consent embodies the three fundamental principles of research ethics, recognizing the capacity and rights of a person to make informed choices. It is an obligation to obtain appropriate informed consent from participants in a research study before participation 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

Informed consent must be seen as a process rather than the preparation of a document and its presentation to the potential participant. It requires the participation of numerous people, including researchers, RECs, and community representatives.



Informed Consent as a Process

Informed consent is not merely a legal requirement or a document to be signed; **it is a communication process between the research team 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.

Informed consent is enhanced if the individuals involved in the process have strong communication skills and when appropriate communication tools are used. A person independent of the research team may be involved, particularly during enrollment when the bulk of the information is usually presented and documentation of the consent is obtained. In many settings, particularly in developing countries, social and economic differences between potential participants and physicians creates a power difference that may unduly influence the participant's decision. This can be especially true when the treating physician, the researcher, and the person obtaining informed consent are the same individual.

The type, extent, and method of the proposed informed consent process require the review and approval of an appropriate REC.

Learner/Facilitator Note: The role of the REC is described later in this curriculum.

Informed Consent (before study initiation)

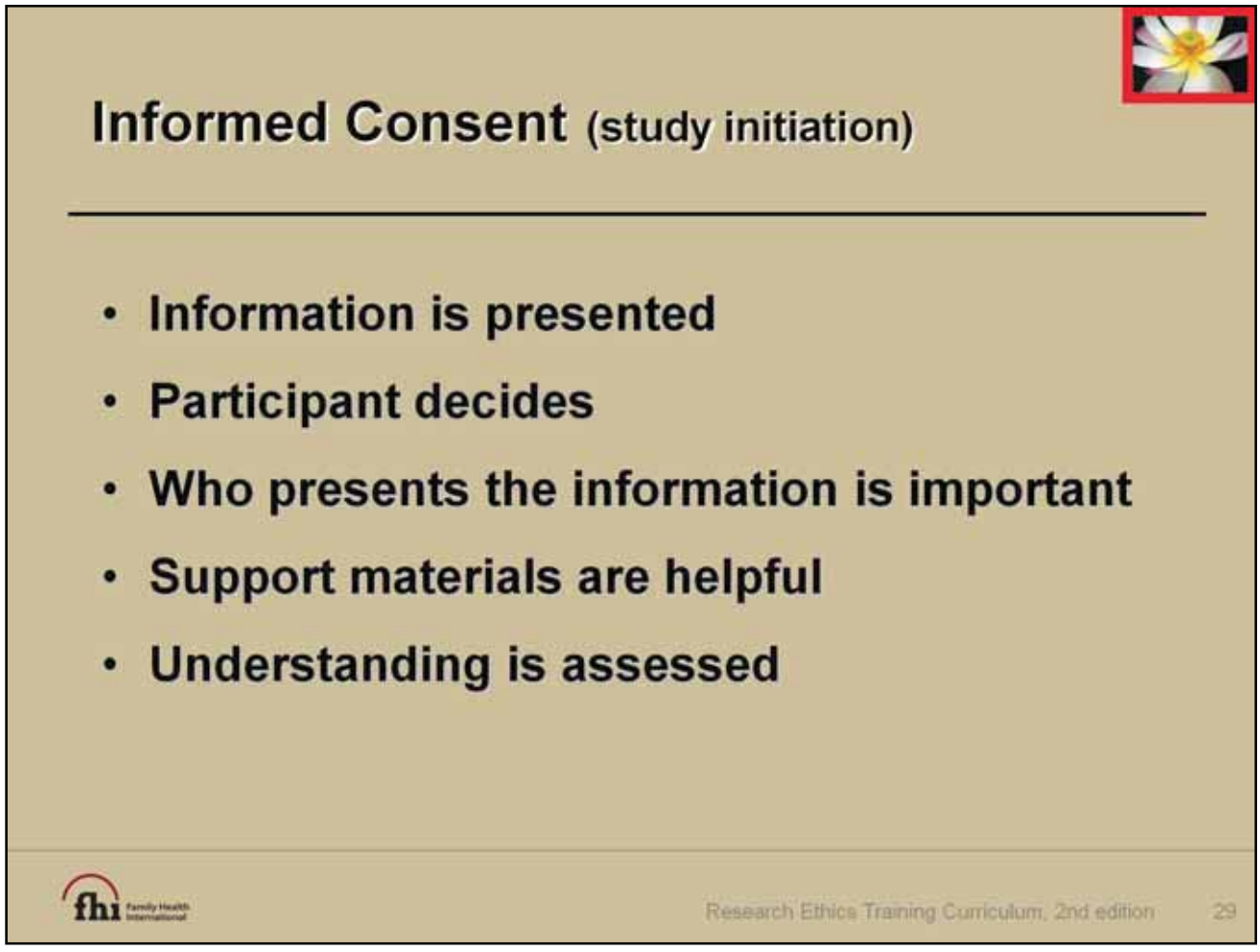
The preparation of the informed consent process must start before the study is actually initiated. The research team should gain a solid knowledge of the characteristics of the locale where the research will be conducted and of any special community (e.g., persons with AIDS) that will participate in the study. Development of the informed consent process should consider the local culture, conditions of local health services, languages, social norms, and conditions special to the type of participants.

Residents of the locale or special community under consideration are the individuals who best know local circumstances. Community representatives may play an important role in advising the research team at this stage. The research team should identify the individuals who will best fulfill the role of community representatives.

The anticipated benefits or risks of the study should be identified before study initiation and be included in the research protocol. The protocol should outline how benefits and risks will be presented to potential participants.

Conducting on-site pilot testing of informed consent documents and approaches may be very informative. Pilot testing provides an opportunity to make corrections or identify better ways of achieving informed consent.

Since the informed research process eventually will have to be reviewed by a local REC, the research team should understand the REC requirements for informed consent.



Informed Consent (study initiation)

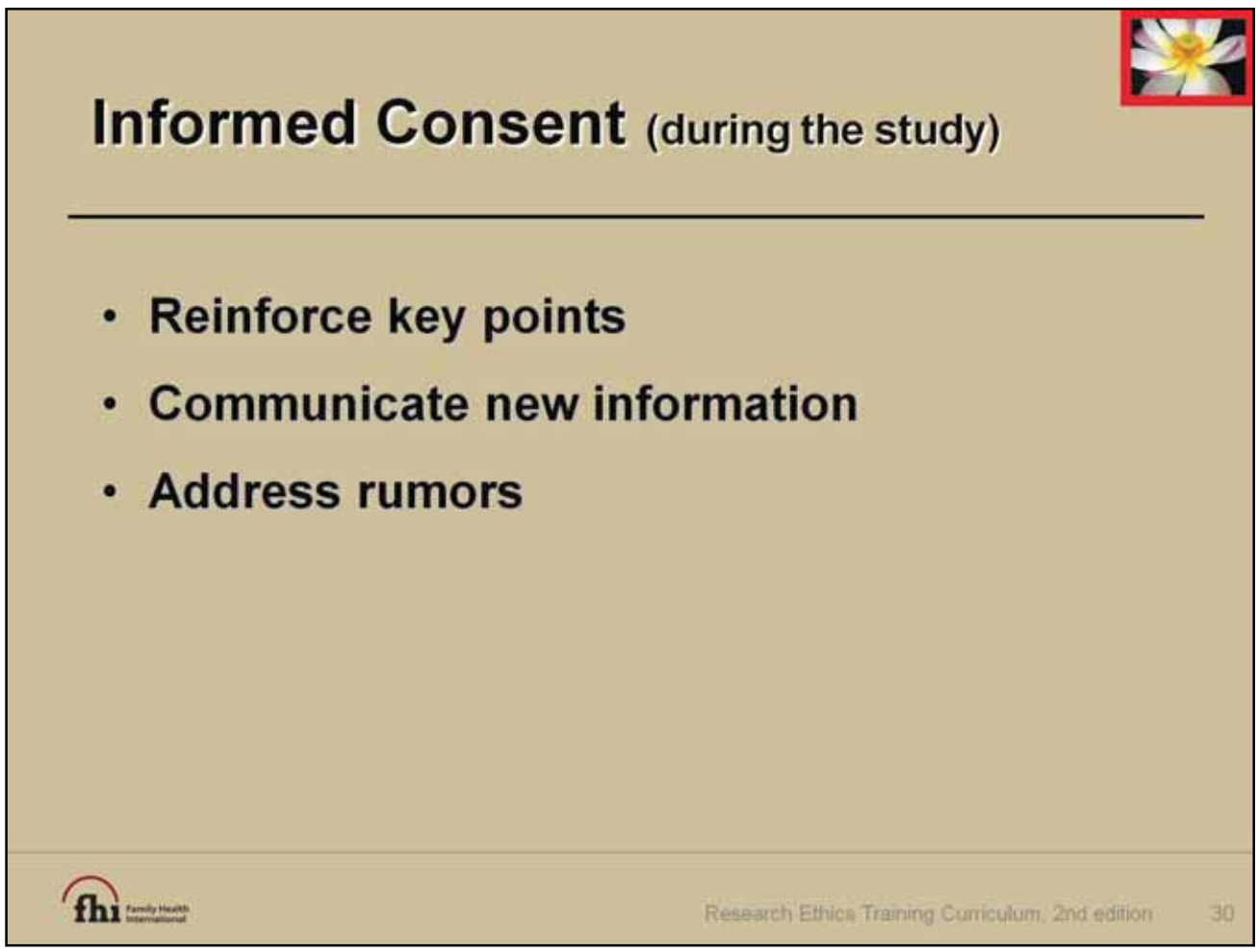
The potential participant typically receives informed consent information during the study enrollment stage. If the material and presentation are well designed, the potential participant understands it and arrives at an informed decision to participate or not. Often, researchers and RECs place most of their attention on this point in the process, focusing on presenting a document to be read and signed by the participant. However, it is unrealistic to expect a person to make an informed decision when presented with so much information in a short period of time. Researchers and RECs must continue to focus attention on the process rather than just securing enrollment.

Who presents the information and obtains the informed consent is an important decision. Often, the researcher is not the best option. He or she may not have strong communication skills or adequate time and might exert an undue influence on the potential participant. Other individuals with communication or counseling skills may be a better option. Some regulations or guidelines require the presence of a witness, who ensures that the required information is presented and also signs the informed consent document.

The use of support materials, such as illustrated forms or videos, is helpful. However, a recent study concluded that the most important factor in understanding informed consent information is the amount of time the presenter spends in direct, personal contact with the potential participant.*

RECs are now increasing attention on evidence that the participant has understood the information, particularly key concepts of informed consent, such as research description, risks, and benefits. Any
problems with understanding must be corrected at this stage.

Learner/Facilitator Note: * Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292(13):1593-1601.



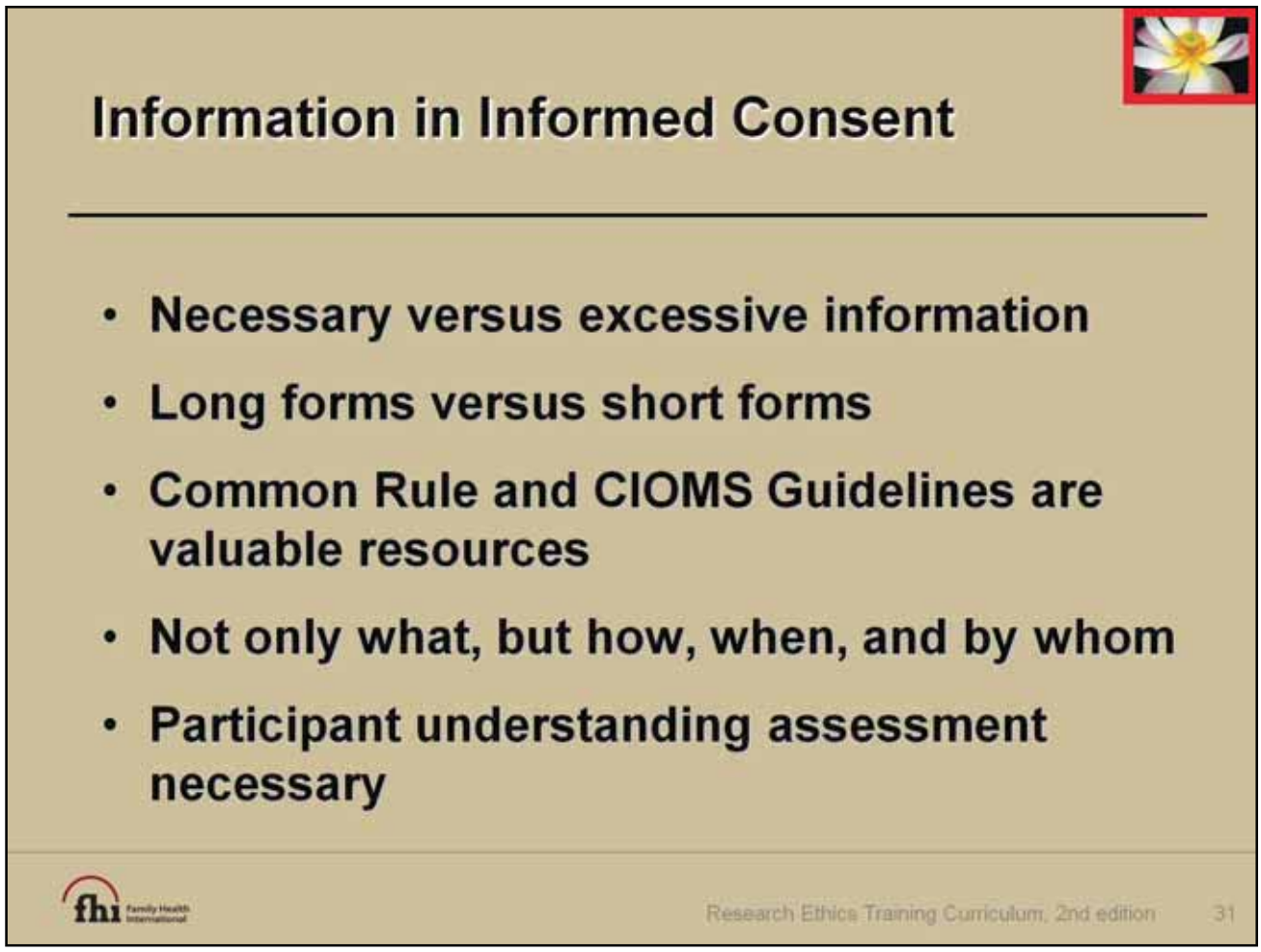
Informed Consent (during the study)

The informed consent process does not end once the participant is enrolled in the study. It continues throughout the research.

The participant receives a lot of information at enrollment that may be forgotten or misunderstood. Key points about the research need to be continuously reinforced. Limited or incorrect understanding of issues such as risks and benefits may negatively impact compliance with the study requirements or cause early withdrawal. The participant may forget that the research is experimental and perceive it as regular health care.

New information may be obtained during the study that changes the risk/benefit ratio. As soon as this information is obtained, it must be presented to the participants and the responsible RECs. In some instances, the REC may require re-consent from all of the participants.

As the study progresses, rumors may arise and cause undue concern to the participants. Such rumors should be corrected as soon as they occur. Community representatives may be helpful in identifying these rumors and advise the research team in the best approaches to correct them, communicating both with study participants and the community at large.



Information in Informed Consent

Deciding what or how much information should be provided in the informed consent materials is very challenging. Providing all of the necessary information to allow the potential participant to arrive at an informed decision is required. However, excessive information may be confusing. "Adequate information," defined as "the amount of information necessary to the individual to make a reasoned decision about whether to participate in the research," is typically proposed. The REC reviewing the research protocol has the final determination of the information to be included. Researchers and RECs may face the difficult decision between a form that is excessively long and difficult to understand or one that is too short to contain all of the necessary information. However, the concept of informed consent as a process allows the research team to identify several stages when information may be provided, thus facilitating understanding.

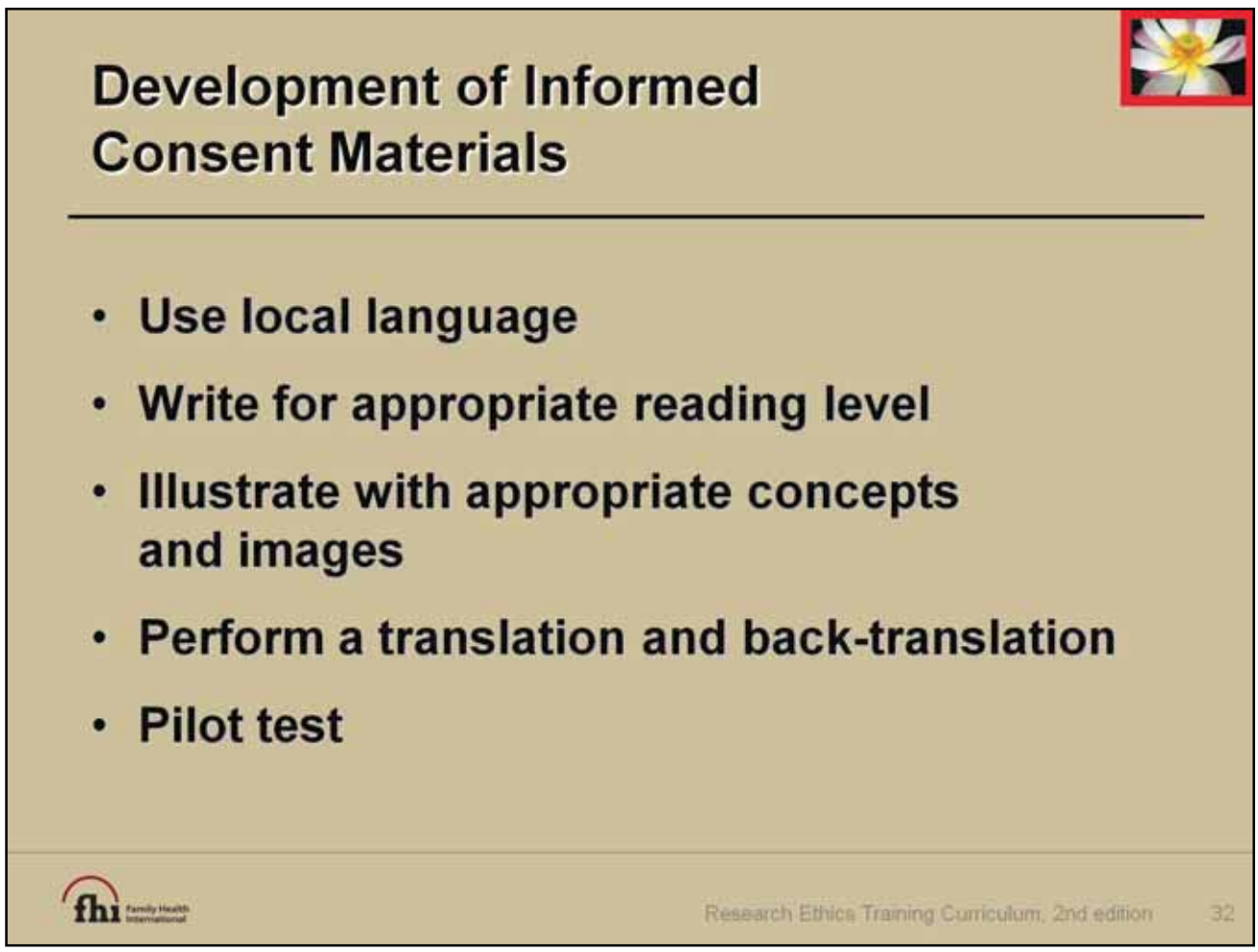
The Common Rule categorizes necessary information into eight basic elements (to be presented in subsequent slides). CIOMS Guidelines propose 26 elements, most of which provide additional guidance on the Common Rule elements. Both documents should be consulted. A recent paper addresses the information that a group of international researchers considers necessary.*

Information on participant understanding of essential information is increasingly being required by RECs. Attention must be given not only to what information, but to how, when, and by whom this information will be provided.

Learner/Facilitator Note: * Rivera R, Borasky D, Rice R, et al. Informed consent: an international researchers' perspective. *Am J Pub Health* 2007;97(1):25-30.

The Common Rule, CIOMS Guidelines, and the Rivera article are recommended reading. Full text of the first two documents may be found in the *Additional Resources* section under *Basic Research Ethics Documents*. The Rivera article is in the *Additional Resources* section under *Selected Bibliography.*

At this point, the self-learner should consider what information is necessary in informed consent materials. For group training, ask the participants to discuss.



Development of Informed Consent Materials

The informed consent process may include different materials, such as the signature form, project fact sheets that explain the study, and flyers or posters that tell about the study.

- Documents must be in the local language, use local terms, and be written for a reading level that potential participants can easily understand.
- Concepts, images, and support materials should be appropriate to the local community.
- Translations should be accurate, of high quality, and be verified by back-translations.
- It is strongly advised that materials and forms be tested for appropriateness before they are used in screening or actual enrollment. This practice, called pilot testing, involves a person who knows the materials and uses them with someone who is very similar to the individuals to be recruited for the study. Based on results from this test, the materials may need to be revised to make them more understandable.

Informed consent is an educational and communication process. Individuals with experience in these fields may be very helpful to the research team.

Community Representation and the Informed Consent Process

Community representatives can offer culturally appropriate guidance when researchers are developing the informed consent process. Their input may improve the cultural or local relevance of the process and materials. They may also help in assessing if the information is understandable.

The information included in informed consent usually reflects the concerns of researchers and sponsors. Thus, information that the potential participant may actually need or expect may not be sufficiently considered or identified. Community input is valuable in selecting the type and sufficiency of this information and how it may best be presented.

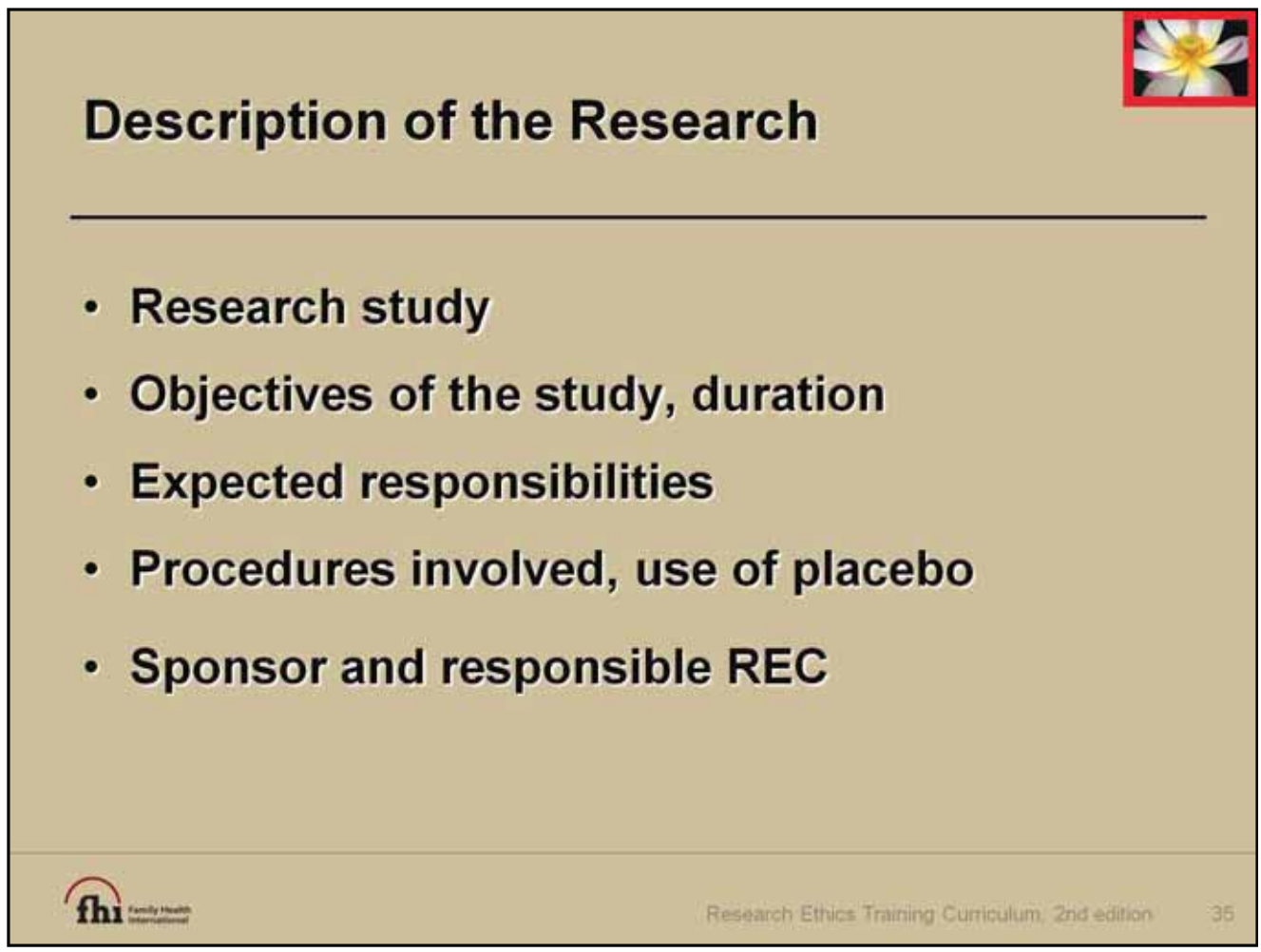
Community representatives may also be given the opportunity to assure that informed consent is conducted in accordance with the approved process.

Essential Elements of Informed Consent

In order to ensure that a research participant receives the necessary information to make an informed decision, the Common Rule proposes the following eight elements as a framework:

1. Description of the research and participant's participation, including identification of experimental procedures
2. Description of reasonably foreseeable risks
3. Description of expected benefits
4. Potentially advantageous alternatives to participation
5. Explanation of confidentiality
6. Explanation of compensation for injuries
7. Whom to contact about the research and participants' rights
8. Explanation that participation is voluntary

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



Description of the Research

Typically, the initial information provided in the informed consent is **a clear, easily understood statement that the study involves research** and is therefore seeking answers to unknown questions. Frequently, participants mistakenly believe that they will be receiving free and effective treatment. The participant must understand that the safety and efficacy of the product being tested is not known and is the reason why the study is being conducted. Some institutions have developed short, generic materials explaining the concept of research and what it means to participate in a research study.

The purpose or objectives of the research must be clearly presented, explaining what new information is sought. The anticipated duration, number of participants, and study sites are also included.

The participant needs to understand what is expected or what she or he will have to do by agreeing to participate in the study. The number and frequency of visits or procedures and requirements for correct use of the study product are included.

Participants must agree to the procedures required by the study, particularly if those procedures are experimental or present some risk. The level of information that participants will receive on the results of laboratory tests or procedures or on the final results of the research need to be included as well.

When the study requires the use of a placebo, the participant must understand that she or he may receive an inactive product or that the therapeutic effectiveness of the active product is not actually known. Placebo and randomization are difficult to explain, and correct understanding must be verified.

The names of the research sponsors and members of the REC that reviewed and approved the research are also commonly included.

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. In some studies or study populations, the social risks may be particularly important and could include stigma, discrimination, loss of respect, or public ridicule.

The amount of information on possible risks, and how it is presented, requires special consideration in the planning of the informed consent process. The probability and severity of risks need to be explained in understandable terms. Whether to present any possible risks or only the most frequent or severe is a decision to be made by the researchers and the REC. The point of view that any possible risk needs to be presented is sometimes guided by legal concerns. A similar decision has to be made about the side effects that may be associated with the product under study.

What is considered a risk or side effect, and whether it is severe, differs from culture to culture. Therefore, cultural context should be considered when deciding how to present this information.

If any new risks are identified during the research, the informed consent must be revised and all of the participating individuals must be notified promptly.

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

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 individuals into participating in the research study. Any free provision of health services to which the participant is otherwise entitled must not be presented as a special benefit. This is particularly important when participants have limited access to health care services due to social or economic reasons.

Special care is needed in determining how benefits are presented to individuals with limited access to health care services. Offering free health care to individuals who would otherwise not have access to it is a powerful incentive to participate in a research study and is potentially coercive. Researchers are responsible for ensuring that potential participants' decisions are not clouded by the promise of health care. Participating in a research study to establish the safety and efficacy of a new product is very different from receiving health care services.

Information about benefits or services to be available to participants when the research has ended should be described in the informed consent form. CIOMS Guidelines include "whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research." If benefits will not be available, that information should be explicit.

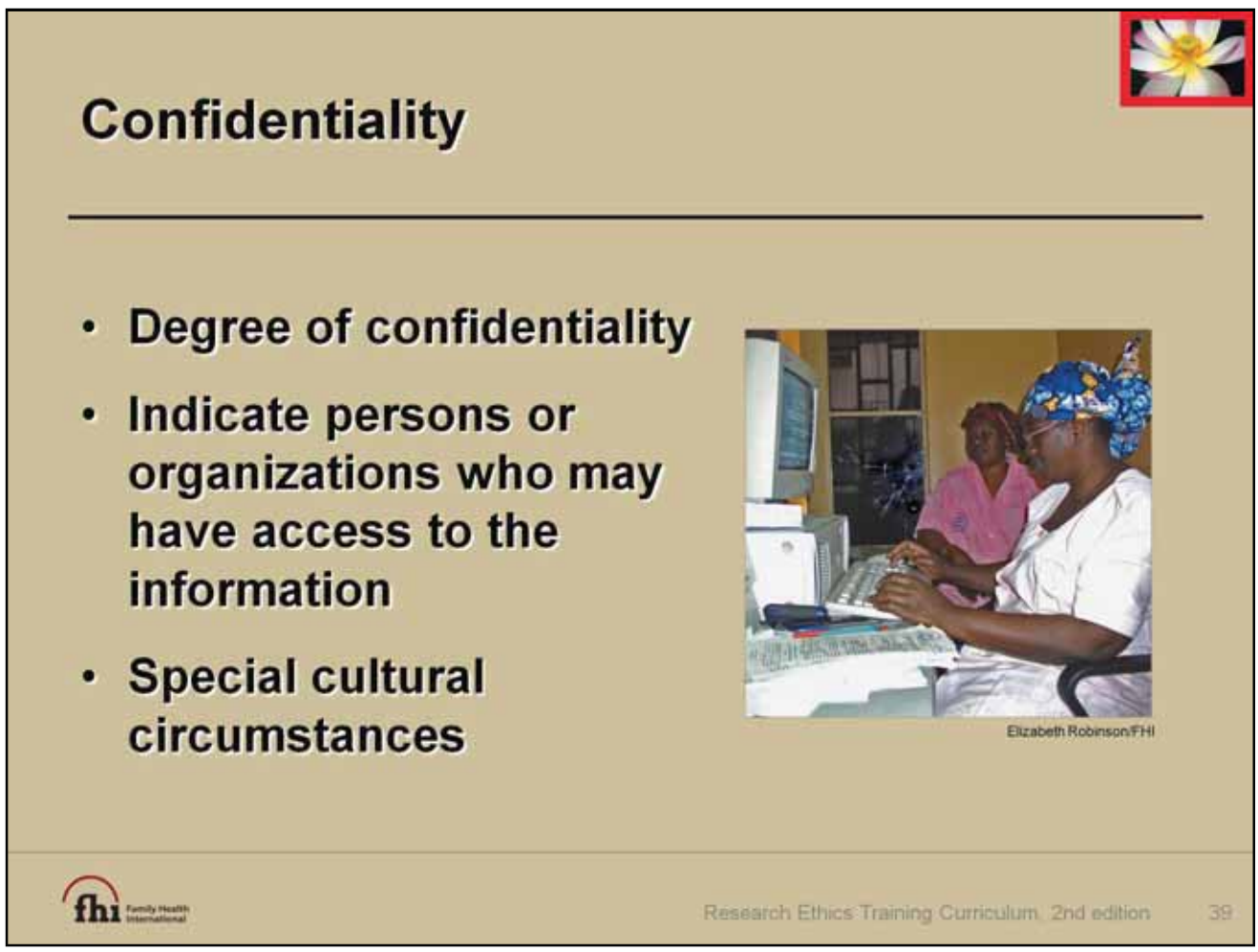
Information on any anticipated benefits to the community participating in the research should also be included. CIOMS Guidelines say to include "the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge." For research on new products, be particularly careful to say if the community will benefit by the access to the study product.

Available Alternatives

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 are available or may be made available—including other options to participating in the research.** CIOMS Guidelines specify "any currently available alternative treatments or courses of treatment."

Descriptions of alternatives should enable the participant to choose between research products or procedures and standard treatments or procedures. For some studies, the only alternative may be not to participate.



Confidentiality

Confidentiality must be considered "as an agreement between the participant and the investigator about how the participant's data will be handled and to whom it will be disclosed." The informed consent form should indicate the degree of confidentiality that will be provided; the names of people or organizations that may review or have access to the research records, such as sponsors or regulatory agencies; the conditions in which the information will be kept confidential; and how long the records will be kept after the study ends.

If the researcher's ability to protect any confidential information is limited, the extent of this limitation must be disclosed to the potential participant. CIOMS Guidelines say to mention information on "the limits, legal or other, to the investigator's ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality."

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.

This section of the informed consent document is sometimes used to describe any anticipated future use of the information or tissue samples collected during the study, including requisites for use such as the need for REC review and approval. The participant must be given the opportunity to consent on the future use of tissue samples and to be contacted again once the study is finished.

Learner/Facilitator 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.

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. CIOMS Guidelines recommend being clear about "the extent of the investigator's responsibility to provide medical services to the participant."

The CIOMS Guidelines also 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 compensation in such cases. The possible lack of compensation or health care for research-related complications must be carefully assessed by the REC reviewing and probably approving this research.

It is generally considered appropriate to compensate participants for their time, travel, and inconvenience. The amount of this compensation should be reasonable, based on local costs, and commensurate with the extent of participation.

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.

Learner/Facilitator Note: What would you consider undue or inappropriate compensation?

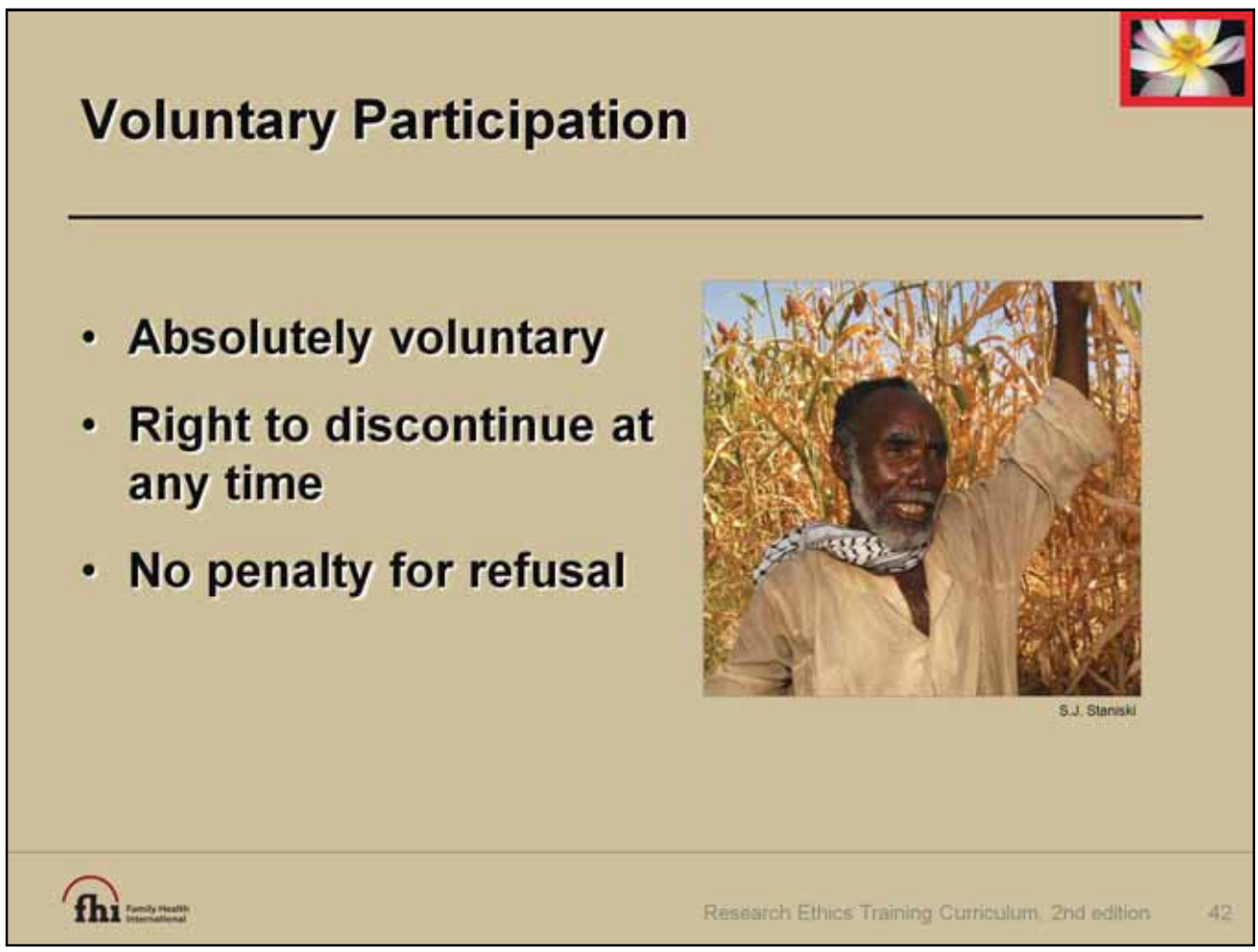
Participant Contacts

In the informed consent form, information must be provided on whom to contact if a research-related question arises or if any side effects, injuries, or complications occur during the conduct of the research. A member of the research team is the typical contact person.

Information must also be provided on whom to contact for questions related to the participant's rights. This contact should not be the researcher or any other person directly related to the study. A member of the REC would be an appropriate contact person.

In general, a list of possible contacts—such as the principal investigator, other members of the research team, REC members, or Community Advisory Board members—should be considered for each particular study.

Contact information should be realistic, economically viable, and culturally appropriate. How contact is to be made should be considered before deciding to include addresses, telephone numbers, and e-mail addresses. As much as possible, contact persons should be available at all times.



Voluntary Participation

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

Documentation of Informed Consent

An informed consent form is commonly used to facilitate and standardize the process of informed consent. The form also provides the physical site where informed consent may be documented, as approved by the REC. An important step in the process of informed consent is the signing, or other type of evidence, that documents the consent. All guidelines encourage written documentation as much as possible.

However, **a signature does not necessarily 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 need for documentation will vary according to the specifics 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 REC responsible for the study determines and approves the method of documenting, or not documenting, informed consent.

Waiver of Informed Consent

Although it is ideal to have an informed consent document that contains all recommended elements, there may be special research situations where it might not be necessary. For some types of research—such as anonymous survey methods, stored tissue research, or retrospective analysis—some of the elements may not apply. In such cases, the REC may allow a waiver of informed consent that permits the researcher to delete some or all of the required elements.

The Common Rule provides four 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 cannot 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 REC when the protocol is submitted for review.

Summary—Informed Consent

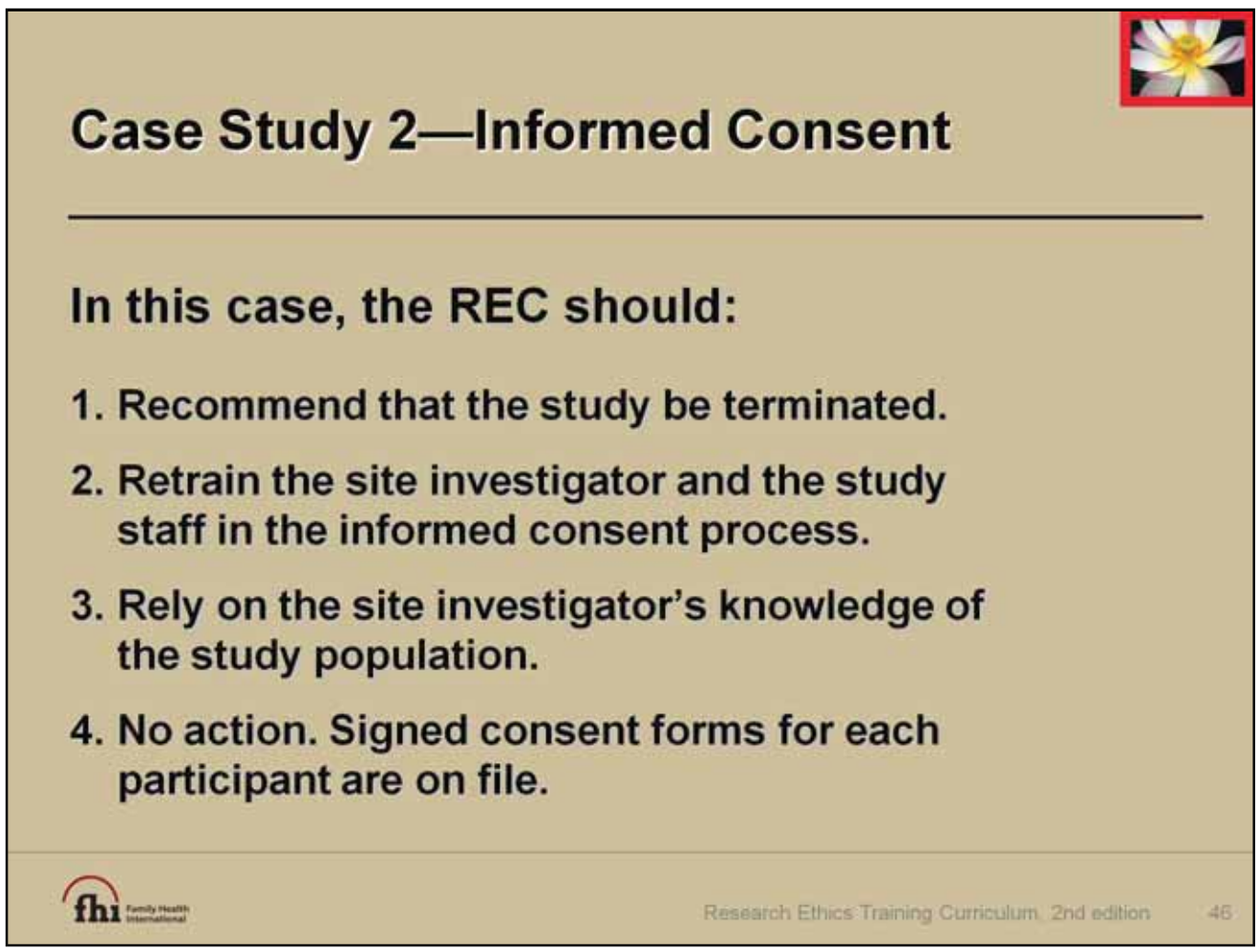
Obtaining appropriate informed consent is necessary before any research is initiated. However, **informed consent should not be seen merely as a legal or regulatory requirement, but as an ethical obligation, designed to protect the basic human rights of research participants.**

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 health condition, education, maturity, and cultural environment have a strong effect on one's ability to understand such information. A signature on the informed consent document is not evidence of having understood the 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. Pilot testing the informed consent materials and process should be considered prior to the study initiation.

The informed consent process must be adapted to local culture and norms, and the use of local language is essential. The participation of community representatives in developing this process is very valuable.

Informed consent must be obtained, without coercion or manipulation, before any prospective participant is enrolled in the study. 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 with no direct interest in the research study. Vulnerable participants require special protections.



Case Study 2—Informed Consent

Question:
In this case the REC should:

1. Recommend that the study be terminated (not allowed to continue).
2. Retrain the site investigator and the study staff in the informed consent process.
3. Rely on the site investigator's knowledge of the study population.
4. Take no action. Signed consent forms for each participant are on file.

Learner/Facilitator Note: At this point, the self-learner should review the case study, included in the *Case Studies* section. The facilitator should have made copies of this case study to hand out to each of the group training participants. The Facilitator should also have carefully reviewed the instructions in the *Case Studies* section.

IV. Responsibilities of Research Ethics Committees

The learning objectives for the *Responsibilities of Research Ethics Committees* section are to:

- Describe the role, composition, and function of Research Ethics Committees
- Comply with the requirements of the Research Ethics Committee in the development and conduct of a research study

Researchers must have clear knowledge and understanding of the responsibilities of RECs and conduct research in strict compliance with the requirements of RECs.

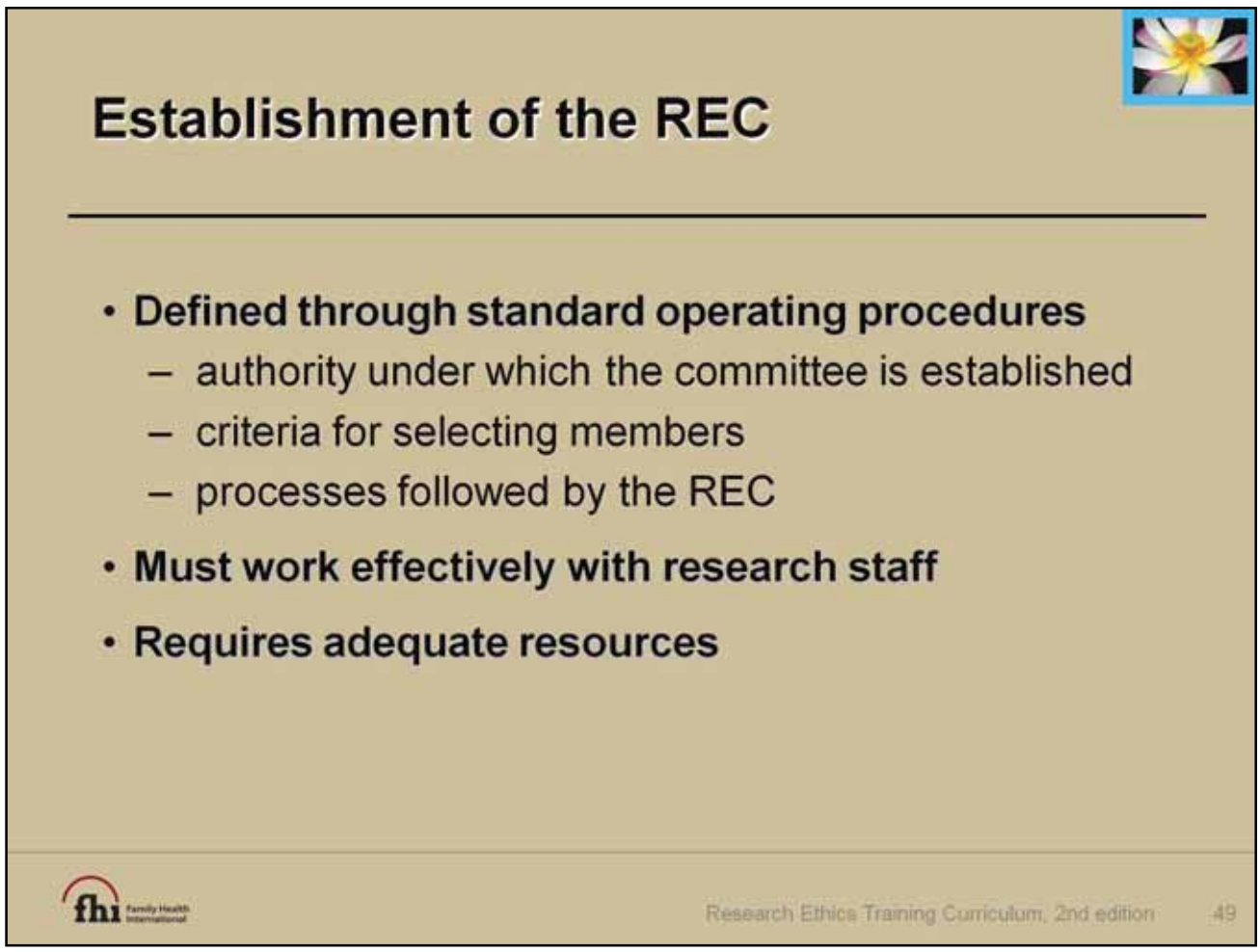
Research Ethics Committees

In contemporary research ethics, it is expected that all research with human participants will undergo review and approval by an independent REC prior to the start of the research. The REC review and approval process and its decisions must be totally independent of the organization that houses and may provide support to the REC.

Ethics committees exist under a variety of titles, including Research Ethics Committee, Institutional Review Board, Ethics Review Committee, Ethics Review Board, Health Research Ethics Committee, and many others. The World Health Organization refers to these groups as Ethics Committees (ECs) or Research Ethics Committees (RECs). We have used the latter term in this curriculum.

Regardless of its name, the committee's primary responsibility is to **review research to ensure the protection of human participants through the application of the three principles of research ethics. Ideally, the REC's review should be guided by its own guidelines or standard operating procedures (SOPs).**

Learner/Facilitator Note: The full text of the WHO Operational Guidelines for Ethics Committees That Review Biomedical Research is included in the *Additional Resources* section under *Basic Research Ethics Documents*.



Establishment of the REC

Sponsors, institutions, and researchers are responsible for the ethical review of the research. There are different ways to accomplish this, including organizing an REC within an institutional structure, contracting with an independent or commercial REC, or establishing a national or regional REC. No matter what type of REC is used, it is imperative that the committee maintain a high level of independence from the institution with which it is affiliated. The REC's decisions cannot be overruled by the institution.

To be effective and consistent, the REC must develop SOPs that define the functions of the REC. SOPs should include the:

- Authority or jurisdiction of the REC
- Criteria for selecting members
- Processes followed by the REC

The REC must also work with research staff in a collegial manner. RECs should provide clear expectations to the research staff and require well-defined procedures for submitting research proposals to the REC. Feedback should be timely and constructive, with well-defined and concrete reasons to support determinations.

To work effectively, **the REC must receive sufficient resources to support its ongoing operations.** The institution must demonstrate to research staff that the REC is an important and respected part of the research program.

Ethics Committee Members

In order to properly review a research proposal, the members of an REC must have various characteristics that will allow them to assess the many facets of the proposal. The review and approval process is the summation of the contributions and experiences of REC members.

First, members of the REC should have basic training in research ethics. This is very different from professional ethics or medical ethics; even members with training in those areas will need to receive training in the application of research ethics.

Second, the REC must be a multidisciplinary group that can understand different types of research. It is rare that an REC always reviews research on the same topic. In cases where a research proposal is beyond the expertise of an REC, it may consider using a consultant to assist in the review. All members and consultants must disclose any potential conflict of interest. Consultants and members with a conflict of interest should abstain from participating in the final review and approval of those studies. To avoid any possible conflict of interest, some RECs have at least one or more members who are not staff of the organization to which the REC is affiliated.

It is important that an REC be diverse in culture and gender so that sensitivities to social issues are not overlooked or underestimated. Diversity will promote a balanced review of the research.

While no committee can represent all elements of the community where research will be conducted, the REC must be capable of assessing the impact of research on the community and determining whether the research is relevant in the local setting. This often leads to the inclusion of REC members who do not have a scientific background but are professionally grounded in the community, such as a member of the clergy, social worker, teacher, or nurse. The inclusion of those who are considered community representatives is now receiving increasing attention. Though community representatives are usually nonscientists, they should exhibit commitment, knowledge, and concern for their communities. The nonscientific and community representative members must be given the same level of respect as their scientific counterparts.

Finally, an REC member must be willing to volunteer time and effort, as most REC work is done voluntarily. Unwilling members who have been assigned by their institutions may not be effective. Institutions can help by showing appreciation and respect to the REC and its members.

Learner/Facilitator Note: List criteria to consider when selecting REC members.

Research Ethics Committees: Criteria for Review and Approval

To approve a research project, the REC must examine the proposed research thoroughly. The criteria for review and approval must be part of the REC SOPs and be known by the researchers. **At a minimum, the REC should address six core issues:**

Scientific design and conduct of the study. The REC should consider how the design of the research 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, or other formal scientific review mechanism, for methodological, technical, or scientific aspects prior to REC submission. At present, the level of responsibility of RECs for the review and approval of the scientific design is being widely discussed. Most RECs continue to have the dual responsibility of reviewing and approving both the scientific and ethical aspects of the research. However, many research institutions have relieved the REC of the scientific review. In such cases, the REC maintains the right to question or discuss scientific issues.

Recruitment of research participants. The REC should examine the materials and methods by which participants will be recruited. *Are the recruitment methods appropriate for the research setting and population? Is the recruitment of vulnerable participants justified? Are there appropriate safeguards 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 REC 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?*

Learner/Facilitator Note: What level of scientific review does your REC conduct in its review of protocols? Do you think there should be a prior scientific review?

Research Ethics Committees: Criteria for Review and Approval (continued)

Care and protection of research participants. The REC must examine the impact of the research on the participants. *Are adequate measures in place to provide for the well-being of participants 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 the necessary elements of informed consent present, such as the description of the research and the participant responsibilities, the risks and benefits of participation, and the right to end participation at any time? What process will be followed to ensure informed consent? Who will conduct it, when, and how? How will informed consent be documented?*

Confidentiality issues. The REC must review how the research team will protect the confidentiality of participants. In some research, the greatest risk could be a breach of that confidentiality. *Are adequate measures in place to protect confidentiality? Will participants be at risk if confidentiality is broken?*

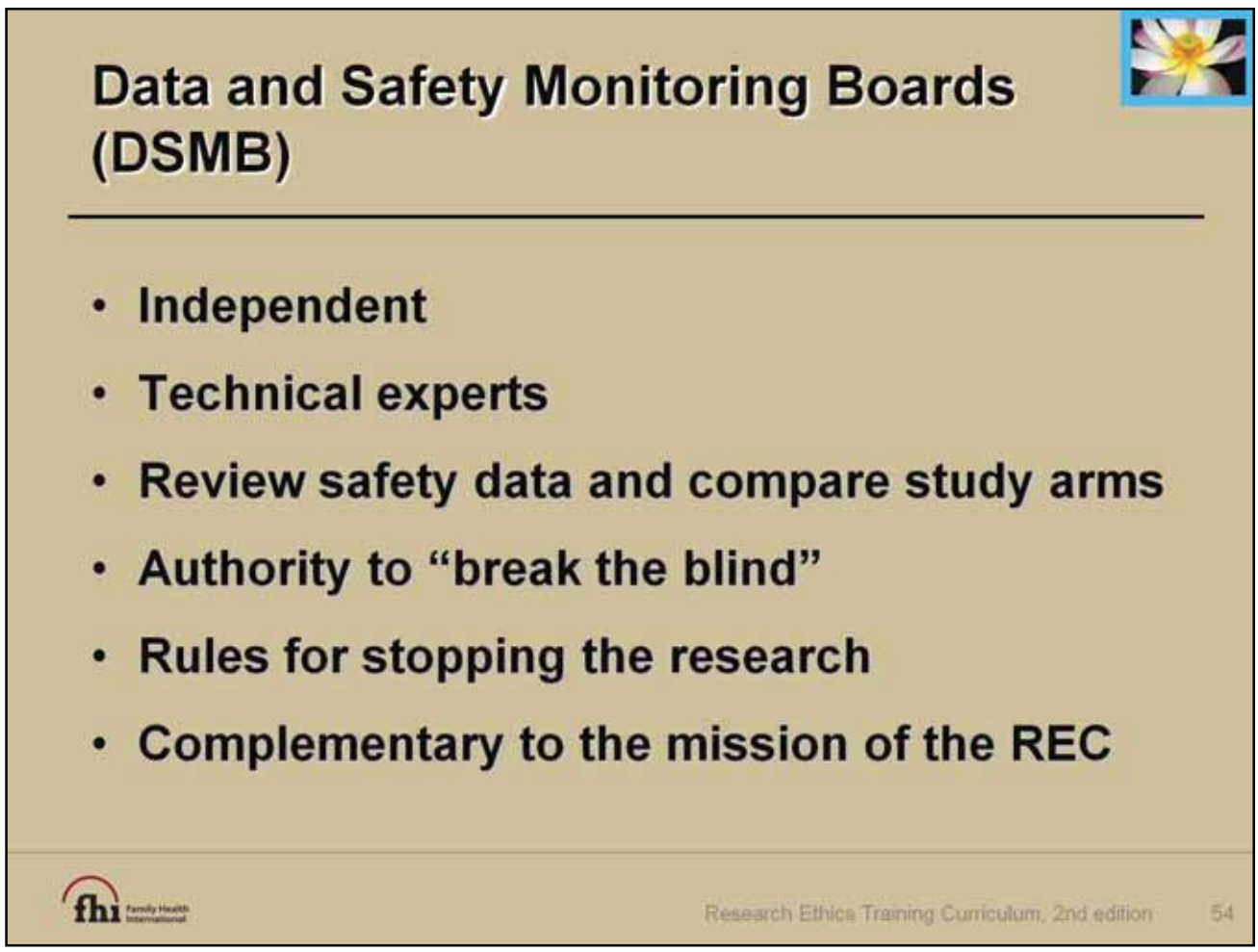
The REC should grant approval only when all of these questions have been answered.

Research Ethics Committees: Additional Responsibilities

Although the REC has been associated mostly with initial review of research involving human participants, the contemporary REC can remain involved throughout the study. Additional functions include:

- Conducting regular review of ongoing research. An REC must review approved research studies at least once per year. More frequent reviews may be mandated by the REC; frequency of review should be commensurate with the anticipated level of risk of the studies. During a review, the REC should be apprised of the status of the research, recent findings related to participant safety, and problems encountered in the research. The informed consent documents should be reviewed to ensure that they continue to provide adequate information to study participants.
- Reviewing all modifications and amendments to approved research. Any change, amendment, or modification to REC-approved materials must be submitted for review and approval prior to implementation. This includes not only the protocol and informed consent documents, but also recruitment materials, data collection instruments, and clinical investigator brochures.
- Monitoring active research studies for compliance. Increasingly, RECs are actively monitoring approved research studies for quality assurance and compliance with REC approval. Monitoring activities may include observation of the informed consent process, verification of the security of confidential material, and confirmation that the protocol is being followed as approved.
- Investigating problems that could impact the safety of participants. The most commonly reported incident is a serious adverse event (SAE), defined as an event that results in death, is life-threatening, requires hospitalization or prolongs existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. RECs must be particularly careful in their review of SAEs. Unexpected adverse events, defined as events not cited in the Investigator's Brochure, may be a cause for concern. An Investigator's Brochure is commonly used in clinical trials of new products and includes detailed information on the study product. A high number of unexpected adverse events or related SAEs may prompt the REC to suspend a study, pending a special review.

Finally, an REC is obligated to investigate allegations of research misconduct and possible violations of the rights of research participants. When problems are discovered, they must be reported as required by local SOPs and regulations.



Data and Safety Monitoring Boards

Multisite clinical trials, particularly Phase II and Phase III trials, are often reviewed by Data and Safety Monitoring Boards (DSMBs). **A DSMB is a committee that is created to review the data from randomized clinical trials to determine whether it is safe for the study to continue.**

Like the REC, the DSMB must be independent with no potential conflicts of interest. Members of DSMBs are chosen for their technical expertise and routinely include physicians, biostatisticians, clinical trial experts, and ethicists.

The DSMB's primary role is to review the progress of the study, with access to interim analyses and adverse event reports. This may include review of interim effectiveness analyses, safety data by blinded treatment arm, and when necessary, unblinding of the study arms. DSMBs operate according to a strict plan that includes criteria for ending a research study while in progress, if continuation of the study exposes participants to risks that are not reasonable in relation to potential benefits.

In this way, a DSMB complements the work of the REC in protecting participants in research studies from unnecessary risk.

Protecting Research Participants: Other Stakeholders

In addition to the oversight of RECs and DSMBs, ongoing research may be subject to monitoring from several different groups. These groups can include the sponsor of the research, contracted monitoring organizations, regulatory agencies, and institutional departments such as regulatory affairs or research compliance offices. These groups want to ensure that the research is being conducted correctly.

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. Like RECs and DSMBs, sponsors and regulatory agencies have the power to suspend research studies.

In addition to the various groups that have official oversight roles, researchers should be aware that unofficial oversight may occur as well. High-profile research studies may attract the attention of the media and public interest groups that are organized on behalf of selected communities (e.g., people living with HIV/AIDS, women at increased risk for breast cancer, etc.).* The careful development, review, and conduct of a study can help protect against negative public perceptions of the research.

Learner/Facilitator Note: * Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? *PLoS Med* 2005;2(9):824-27.

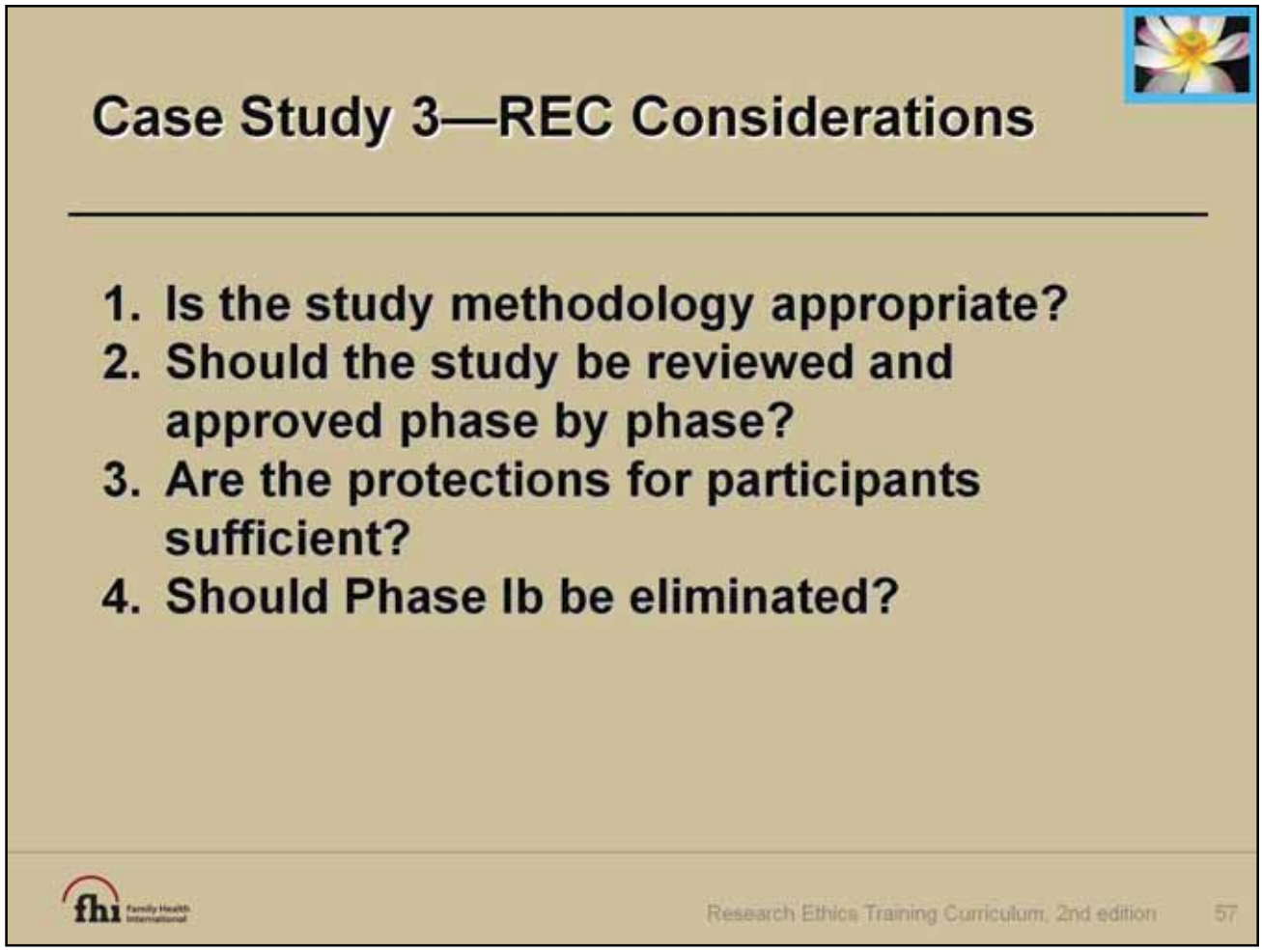
Summary—Research Ethics Committees

In contemporary research ethics, the protection of participants in research studies is a dynamic, multifaceted operation, with many players filling key roles.

Chief among these is the REC, which is viewed as the cornerstone of the process of protecting research participants. The work of the REC may be complemented by additional oversight mechanisms, such as Scientific Review Committees or DSMBs. But, unlike those other mechanisms, there is no surrogate for REC review.

In addition to the official mechanisms of protection, research may be subject to unofficial oversight from the media and public interest groups.

Researchers can minimize the possibility of poor reviews from any of these bodies by carefully planning their research projects.



Case Study 3—REC Considerations

1. Is the study methodology appropriate?
2. Should the study be reviewed and approved phase by phase?
3. Are the protections for participants sufficient?
4. Should Phase Ib be eliminated?

Learner/Facilitator Note: At this point, the self-learner should review the case study, included in the *Case_Studies* section. The facilitator should have made copies of this case study to hand out to each of the group training participants. The Facilitator should also have carefully reviewed the instructions in the *Case Studies* section.

V. Responsibilities of Sponsors and Researchers

The learning objective for the *Responsibilities of Sponsors and Researchers* session is to:

- Comply with the responsibilities of sponsors and researchers in the development and conduct of research studies

In any research study, the sponsor of a study and the researcher who conducts a study have multiple responsibilities related to the protection of study participants. Some of these responsibilities are shared; however, neither can assume that the other will take care of their responsibilities for them.

Sponsor's Responsibilities

Sponsors have a number of important responsibilities in research. While sponsors may delegate the implementation of certain aspects of the research, such as to contract research organizations, they cannot delegate responsibility. At the core of these responsibilities is a commitment to protect research participants. This is accomplished in the following ways:

- Select only qualified researchers.
- Provide them with all of the necessary means to implement the research properly, including methodologically sound protocols, operational procedures, and training.
- Require the review and approval of a properly established REC.
- Promote research integrity by monitoring study sites, managing potential conflicts of interest, and training in issues such as research ethics. In doing so, sponsors discourage scientific misconduct by researchers.
- In some settings, sponsors may also have the responsibility of ensuring the appropriate management of SAEs.

Sponsor's Responsibilities in International Research

In studies taking place in low-resource countries, the sponsor may have additional responsibilities. Sponsors of international research must:

- Comply with all local ethical, regulatory and legal requirements. Sponsors must insist on review by a local REC.
- Prior to study initiation, discuss with local partners the relevance of the research to the local health needs and priorities and the potential benefits of such research for the participating communities.
- Ensure the availability and access to health care services necessary for the safe conduct of the research.
- In many low-resource settings, sponsors may need to build the local technical capacity in order to conduct a study. This can include improving health care and research facilities and providing training to local research staff. In addition, sponsors should collaborate with local institutions in upgrading or developing the capacity of the local REC.
- Following the research, sponsors should try to make the products of the research available to the participants and the host community, in consultation with appropriate local or national institutions. How this will be done, or not done, must be part of the research design.

Researcher's Responsibilities

The researcher has a number of responsibilities, including several related to the protection of the people participating in research. While many of these responsibilities are legal requirements, several are ethical norms that scientists and health care professionals must follow. Like sponsors, researchers may delegate some of the research work to other members of the research staff. However, the researcher retains ultimate responsibility. Responsibilities related to the protection of research participants include:

- The use of scientifically and technically appropriate research protocols, which effectively **place 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."
- Also, the researcher has the obligation to protect the confidentiality of the participants as stipulated in the informed consent. This is very important in research involving populations and conditions or diseases that are stigmatized within the local community.

Researcher's Responsibilities (continued)

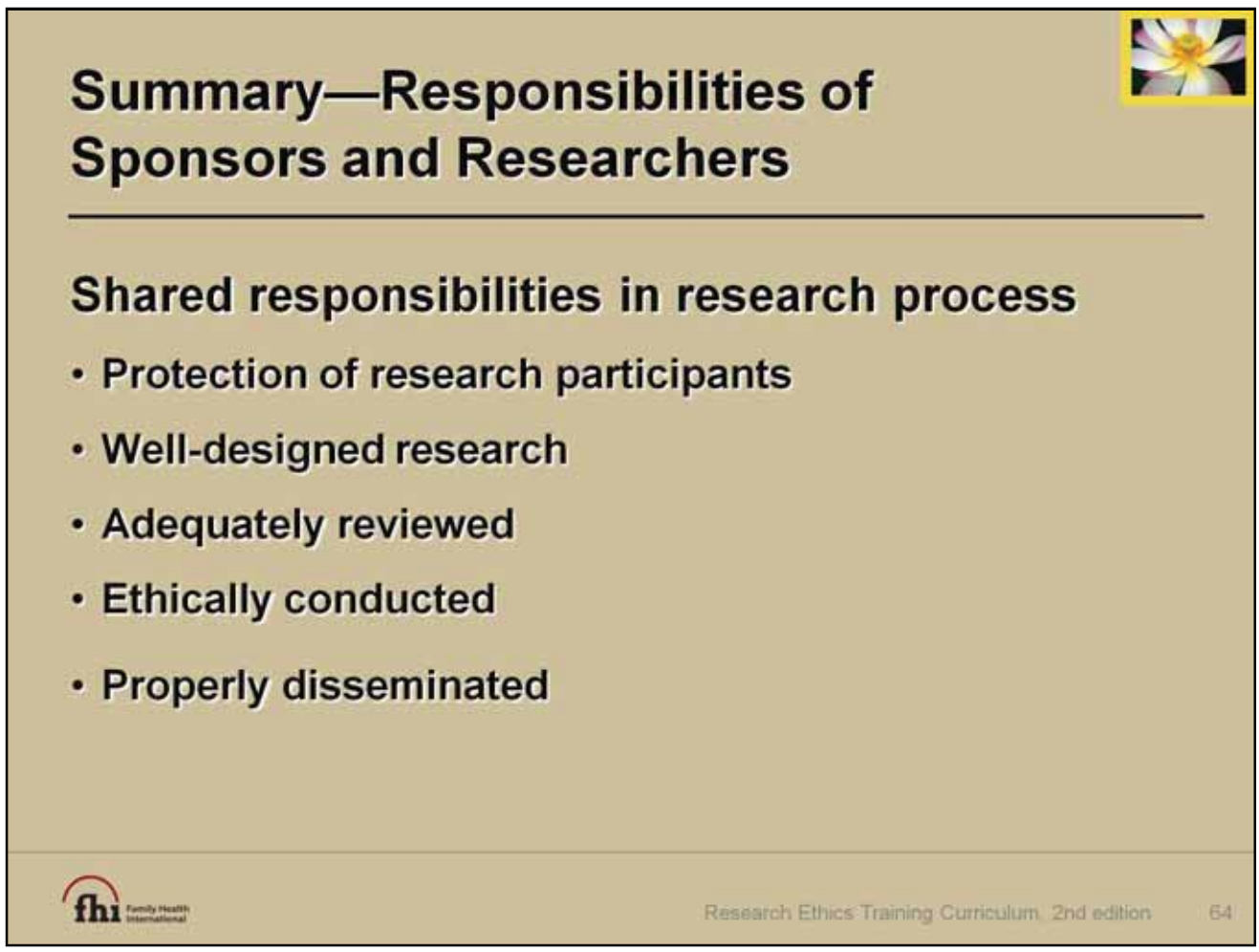
The researcher must conduct the study according to the approved protocol, and may only make changes with prior approval from the sponsor and REC.

- The researcher must conduct the study with integrity. This can be accomplished by providing adequate training for staff, including training in research ethics, and ensuring the integrity of the data through strict adherence to the study procedures. This is also accomplished by being transparent in the identification and management of conflicts of interest.
- The researcher must ensure that an REC will be responsible for the initial and continuing review and approval of the research and must provide the REC with all information necessary to perform these functions. Researchers are responsible for complying with all REC decisions, stipulations, and recommendations. The researcher must report to the REC any adverse events or unanticipated problems involving risks to participants, including protocol violations or any complaints from the participants.
- Increasing importance is being given to the responsibilities of researchers in the continuing protection of participants once the study is concluded, such as the provision of health care for research-related conditions or complications or the facilitation of access to the study product.

Researcher's Human Qualities

In addition to being skilled clinicians and scientists, it is very important that researchers who interact with participants possess certain human qualities, such as:

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

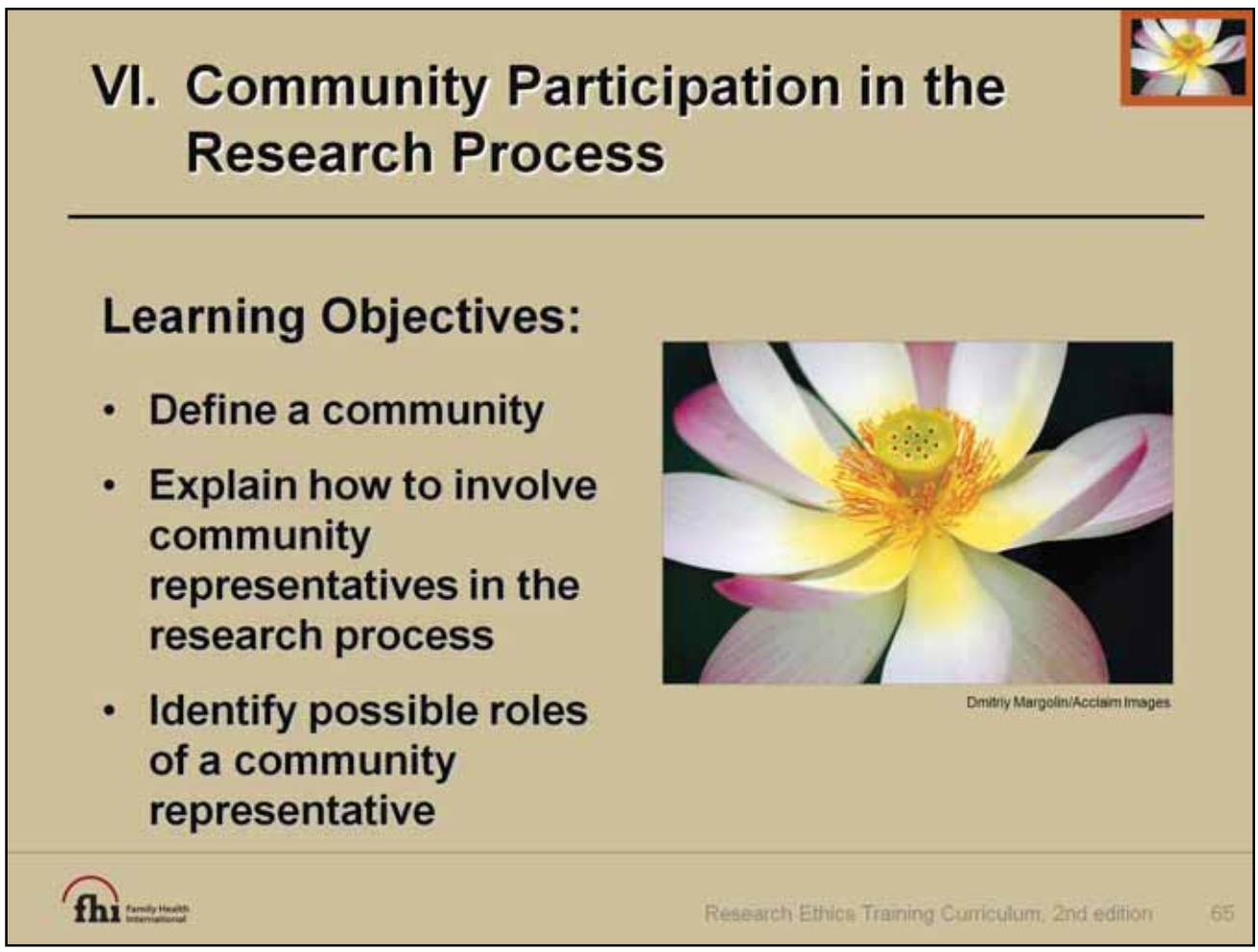


Summary—Responsibilities of Sponsors and Researchers

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

- Protecting the safety and well-being of research participants
- Designing ethical research that addresses a local research 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.



VI. Community Participation in the Research Process

The learning objectives for the *Community Participation in the Research Process* section are to:

- Define a community
- Explain how to involve community representatives in the research process
- Identify possible roles of a community representative

Activity (10 minutes)

Ask participants to discuss these questions:

- What is a community?
- What kind of community is shown in this slide?
- Why is this a community?
- What are some of the communities that you belong to?
- How are these communities defined, or what are the characteristics of these communities?
- What makes you a member of a community?
- Why is it important for you to belong to a community?

Learner/Facilitator Note: Some possible answers are on the following slides.

Characteristics of a Community

In 2001, a study of 118 persons with different social and ethnic backgrounds defined community as "a group of people with diverse characteristics who are linked by social ties, share common perspectives, and engage in joint action in geographical locations or settings."*

One element of community was identified as a "sense of place, something that could be located and described, denoting a sense of locale or boundaries." A community can be an identifiable area or location, such as a city, a village, a neighborhood, or even a workplace.

This study also identified shared interests as part of belonging to a community. As members of a community, we share our values, norms, religion, interests, worries, needs, happiness, and suffering with the other members. Often, these commonalities have existed for years, if not for centuries.

Other identified elements of community were joint actions that bring people together or social ties such as family, friends, and diversity.

Learner/Facilitator Note: * MacQueen KM, McLellan E, Metzger DS, et al. What is a community? An evidence-based definition for participatory public health. *AJPH* 2001; 91(12):1929-38.

Special Research Communities

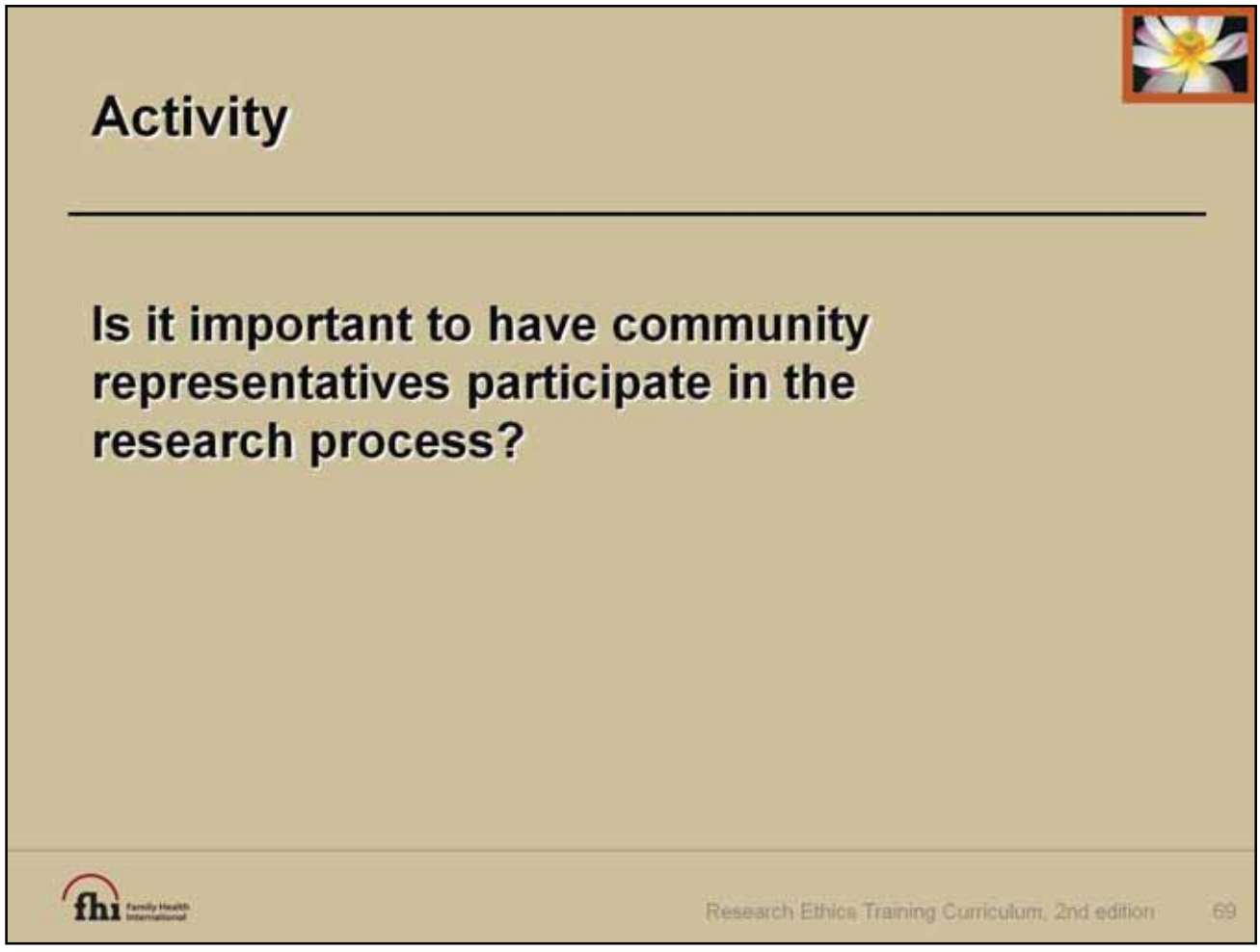
Some studies may target participants who belong to special communities. Examples include:

- Disease. Examples: individuals with AIDS or breast cancer.
- Occupation. Examples: health care providers, teachers, or sex workers.
- Special groups from the same population. Examples: adolescents, prisoners, or injecting drug users.
- Specific geographic community. Examples: an urban city, a small rural village, or a tribal unit.

Regardless of the type of community, representatives should participate in the development, review, and conduct of the research to ensure that the views and needs of such communities are considered.

Often the benefits and risks of the research affect not only the individual participants, but also the entire community from which they are drawn. For instance, the improvement of health care as a result of the research may benefit the entire community. On the other hand, the risk of stigma with some types of research may affect the entire community.

Learner/Facilitator Note: If a study for the development of a new human papillomavirus (HPV) vaccine were to be conducted in the community where you work, what would be the main benefits and risks for the community?



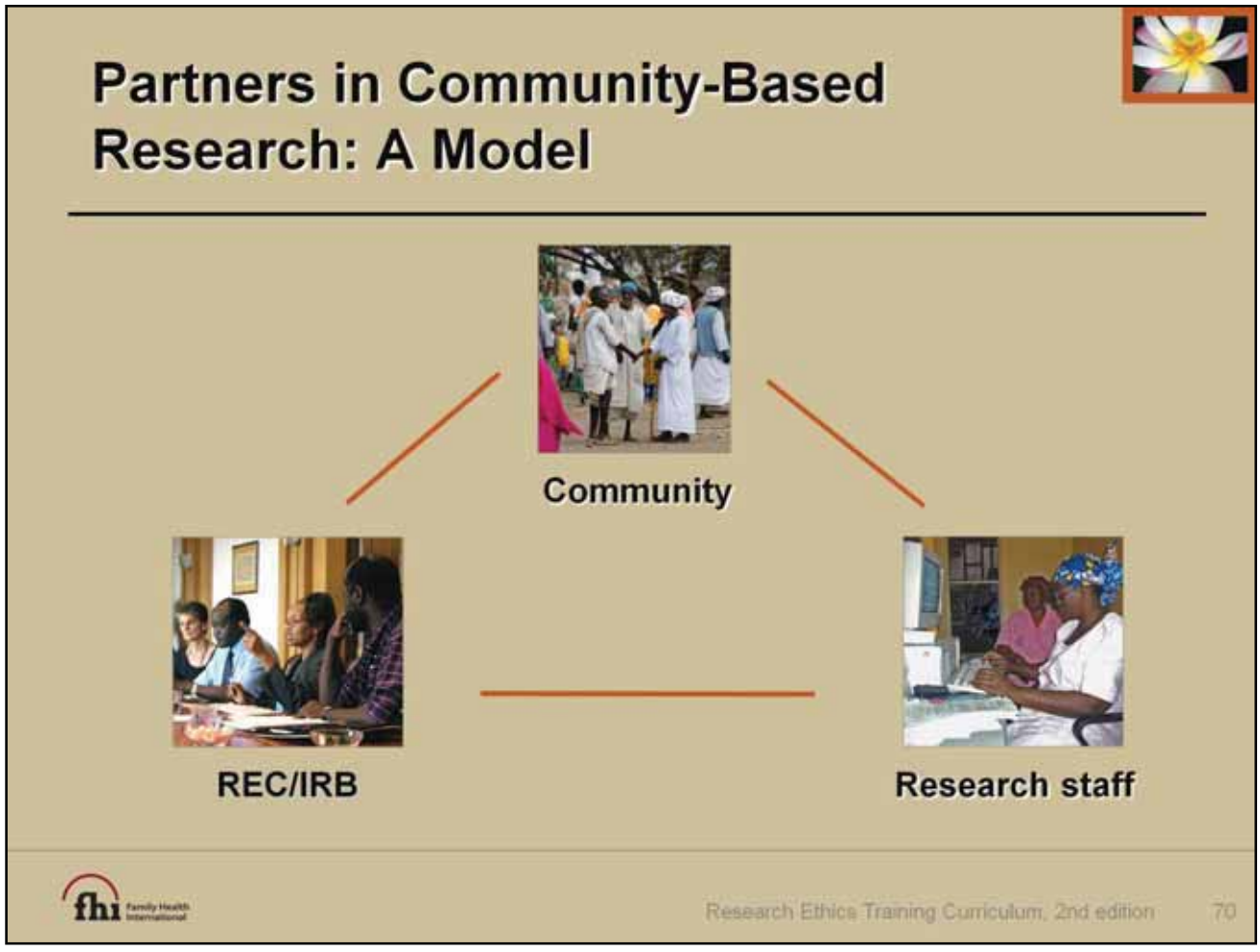
Activity (10 minutes)

The purpose of this activity is to reflect on the role of community representation in the conduct of research.

Ask participants to discuss with a partner for two minutes **why they think it is important to have community representatives participate in the research process.**

Ask each pair to write two reasons on a note card. Have participants post the note cards on a flip chart or tape to a wall. Ask a few pairs to share their answers aloud with the entire group.
Participants can look at all of the cards during a break.

Learner/Facilitator Note: Some possible answers are on the following slides.

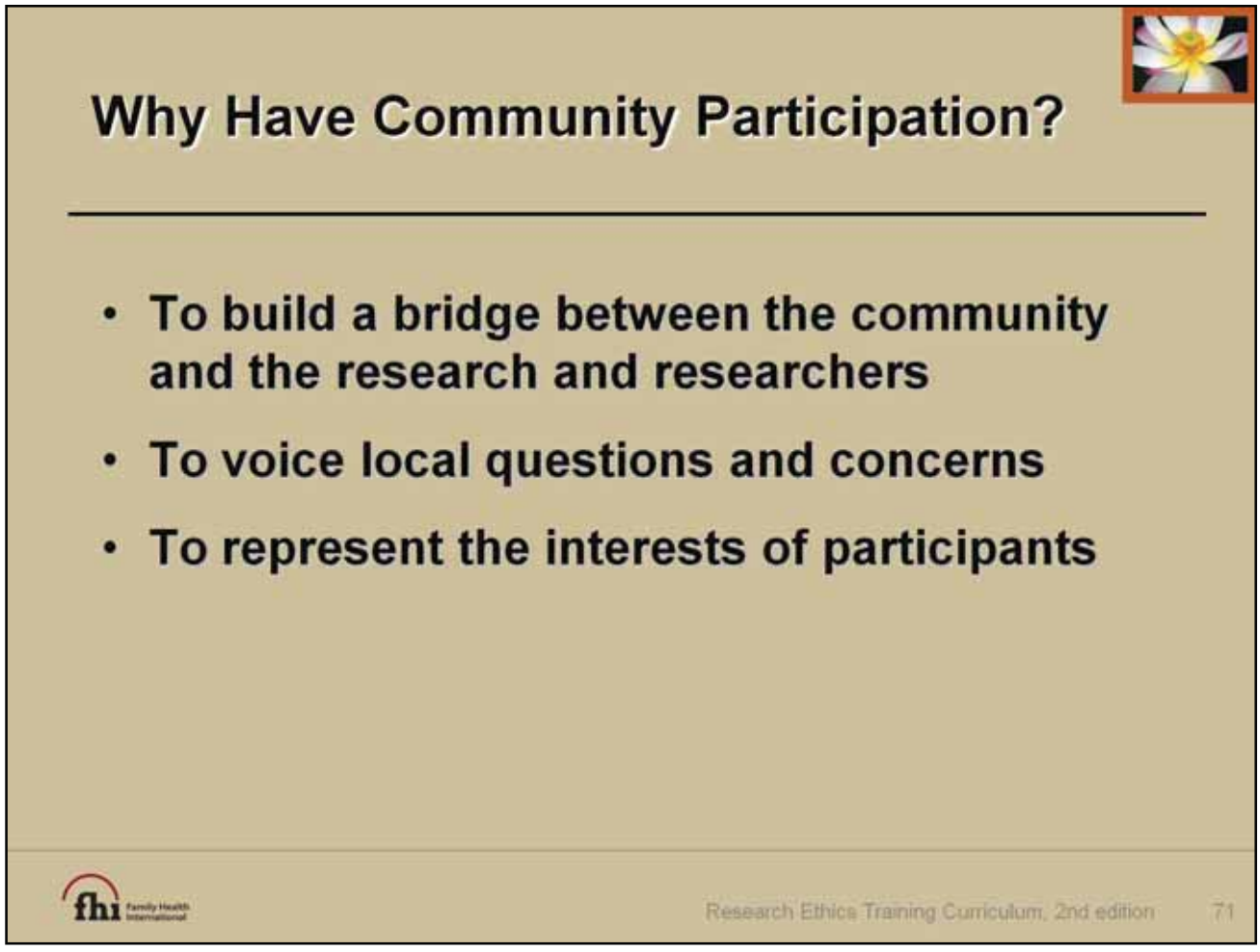


Partners in Community-Based Research: A Model

Many partners may be involved in developing and conducting a research study in a community. A model relationship includes three main partners:

- The community where the research will be taking place, represented by designated community representatives.
- The research staff, including the study investigator and other persons with a direct role in the research. The sponsor of the research is also included here, although this person or organization is not always physically located at the research site.
- The REC or Institutional Review Board (IRB), which reviews and approves the research project to ensure the appropriate protection of research participants.

These three partners should work together to make sure that research studies are conducted with the best interests of the community in mind. All partners have specific responsibilities to each other and to the research process. When all partners have the information and training needed to meet their responsibilities, it is more likely that the research will be conducted successfully and benefit the local community.



Why Have Community Participation?

To build a bridge between the community and the research staff, it is important to involve the community in the entire research process. Community involvement optimizes the protection of research participants, enhances investigators' perceptions of the research goals, and improves the way research is designed. It is also very helpful for the introduction of the research results to the community.

Community participation in the research process can happen in many ways. Sometimes community representatives form a group to advise the research process, as the voice of local questions and concerns. Other times, an REC—formed of members not based in the community—will ask a local community representative to become a member and be a voice for the community or the participants. There are also formally established groups representing the community, such as a community advisory board, community working group, or community advisory group. Such groups are usually empowered to advise the research study team throughout the research process.

Community participation is a relatively new concept. Although established international guidelines recommend community participation, at present they do not detail exactly how to achieve it. Sometimes representation is on a local level; other times, it could be on a national or international level.

Community Participation in the Research Process

At a minimum, community representation should be involved:

- **Before** the study, to inform the community. In health-related research, one of the first steps for community representatives is to agree that the research addresses a need or problem relevant to that community and to confirm that the study design is sensitive to local norms and culture. The study should bring some benefits to research participants or the community. Since research is done to answer questions, there is some risk associated with participation. Therefore, community representation is needed before the research begins to help develop appropriate ways to protect the participants. As already mentioned in Section III, participation of the community in the informed consent process is particularly valuable.
- **During** the study, to follow the progress of the study and address any concerns. Community representatives can continue to educate others about the research. They can also be alert to issues or concerns about the research and communicate them to the research staff.
- **After** the study, to share the findings. Once the research is completed, community representatives can help to make results known and applied to the entire community. Community representatives should understand that there is often a long gap between research and practice, so the sharing of findings may take up to several years.

Responsibilities of Community Representatives

Community representatives may have many responsibilities, depending on the setting and type of research study. One responsibility is to ensure that the research addresses a local need and is not conducted only to find answers to scientific questions, without relevance or benefits for the community. When research is conducted among individuals with a specific disease, community representatives help to make sure that the research design is sensitive to the needs and expectations of the individuals with the disease.

In any type of health research, community representatives are advocates for the well-being of participants.

Community representatives may work with the researchers in the development of the informed consent process to make sure that this process is complete, comprehensible, voluntary, and culturally appropriate.

Particularly important is what treatment participants will receive while in the study and any benefits that might be available once the study is completed. A community representative might ask:

- Will the drug, treatment, or intervention be made available to the participants?
- Who will make it available? Under what conditions?
- How long will it be available in the community where it is tested?
- Will the quality of health care in the community improve as a result of the research?
- Will the research result in desirable behavior change in the community?
- What other benefits will the community receive as a result of the research?

Primary Responsibilities of Research Ethics Committees and Community Representative Groups

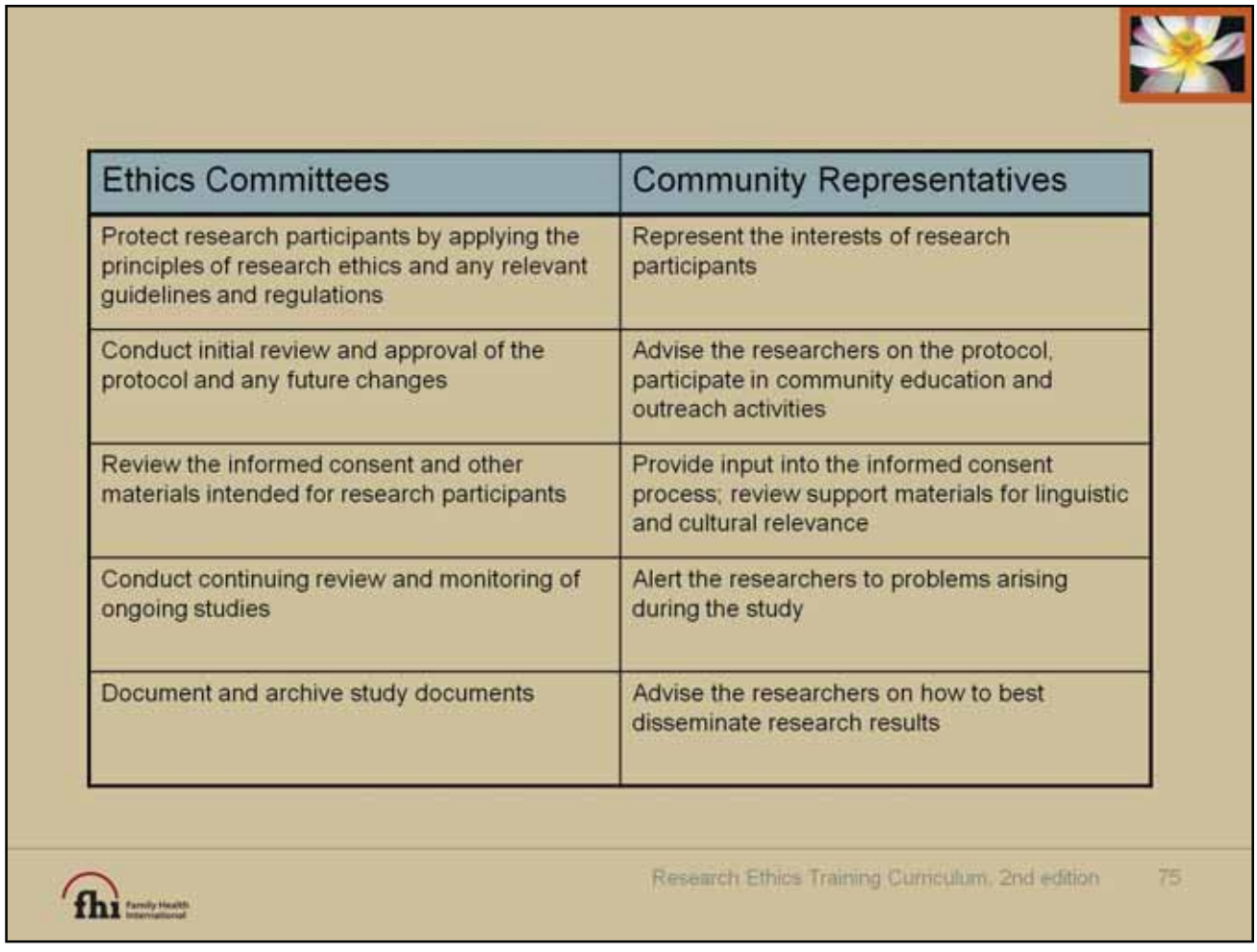
Research Ethics Committees and community representative groups may have shared functions. However, there are basic differences worth noting:

The REC is the only group with the power and responsibility to review and approve the research protocol before the research can be initiated. Community representative groups can only advise the researchers in the development of the research protocol. The same applies to the continuing or annual review of initially approved studies.

Only the REC has the authority to review and approve the informed consent form and process. Community representative groups can play a key advisory role in assuring the linguistic and cultural relevance of the consent form and process.

The establishment of formal or institutional RECs is mandated by all international and national regulations. So far, there is no formal regulatory requirement to establish community representative groups. But the importance of these groups throughout the research process is being increasingly recognized.

Community representative groups provide a valuable role in community education and outreach activities, alerting the research team about rumors or misunderstandings that may develop during the research and assisting in dispelling them and in advising how to best disseminate research results to the community. RECs are not responsible for these important aspects of research.



Primary Responsibilities of Research Ethics Committees and Community Representative Groups (continued)

Some important differences between RECs and community representative groups are:

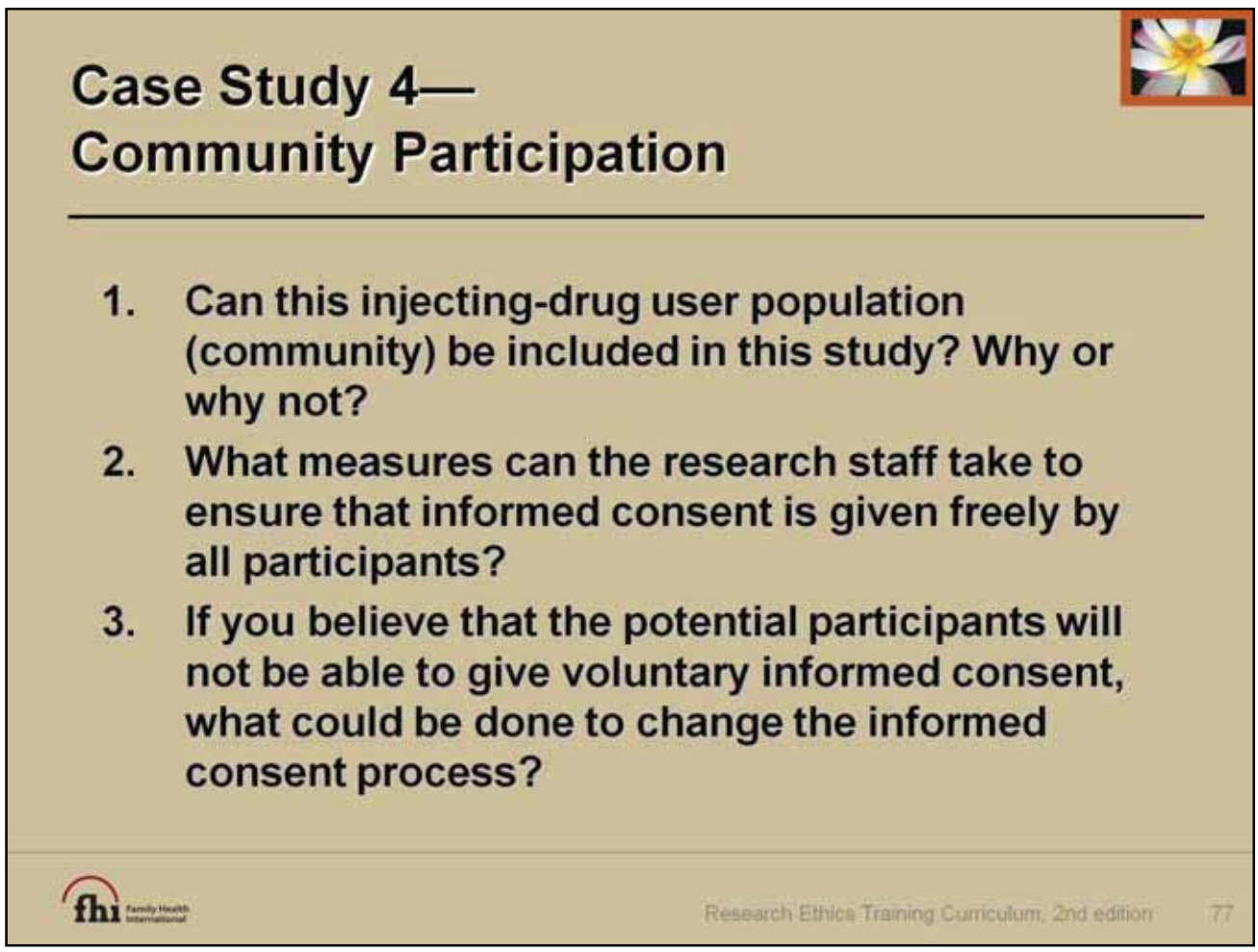
- RECs operate under formal national or international guidelines and regulations. So far, no equivalent guidelines or regulations exist for community representative groups.
- RECs are required to review and approve the research protocol. Community representative groups only have an advisory role. The inclusion of members of the community representative group on the REC is highly desirable.
- The review and approval of informed consent is an REC regulatory requirement. Community representative groups only have an advisory role.
- The continuing review and monitoring of a study is an REC regulatory requirement. Community representative groups only have an advisory role.
- The documentation and archiving of selected study-related materials is an REC responsibility. Community representative groups may play a key role in the dissemination and application of research results.

Summary—Community Participation in the Research Process

A community can be defined as a group of people sharing the same location, beliefs, culture, ideals, goals, age, gender, occupation, lifestyle, or disease. All of us belong to one or more communities, bonded by common interests.

When researchers decide to study a specific community, members of that community can come together to promote their interests, ask questions, and voice any concerns. Community representation can occur individually or in the form of formally established groups who take part in the research at all stages of the study.

Community participation ensures that the research responds to community health needs and expectations, involves appropriate informed consent, and provides access to research benefits. Community participation improves the research and can ensure that studies are developed and implemented in the best interests of science and the community.

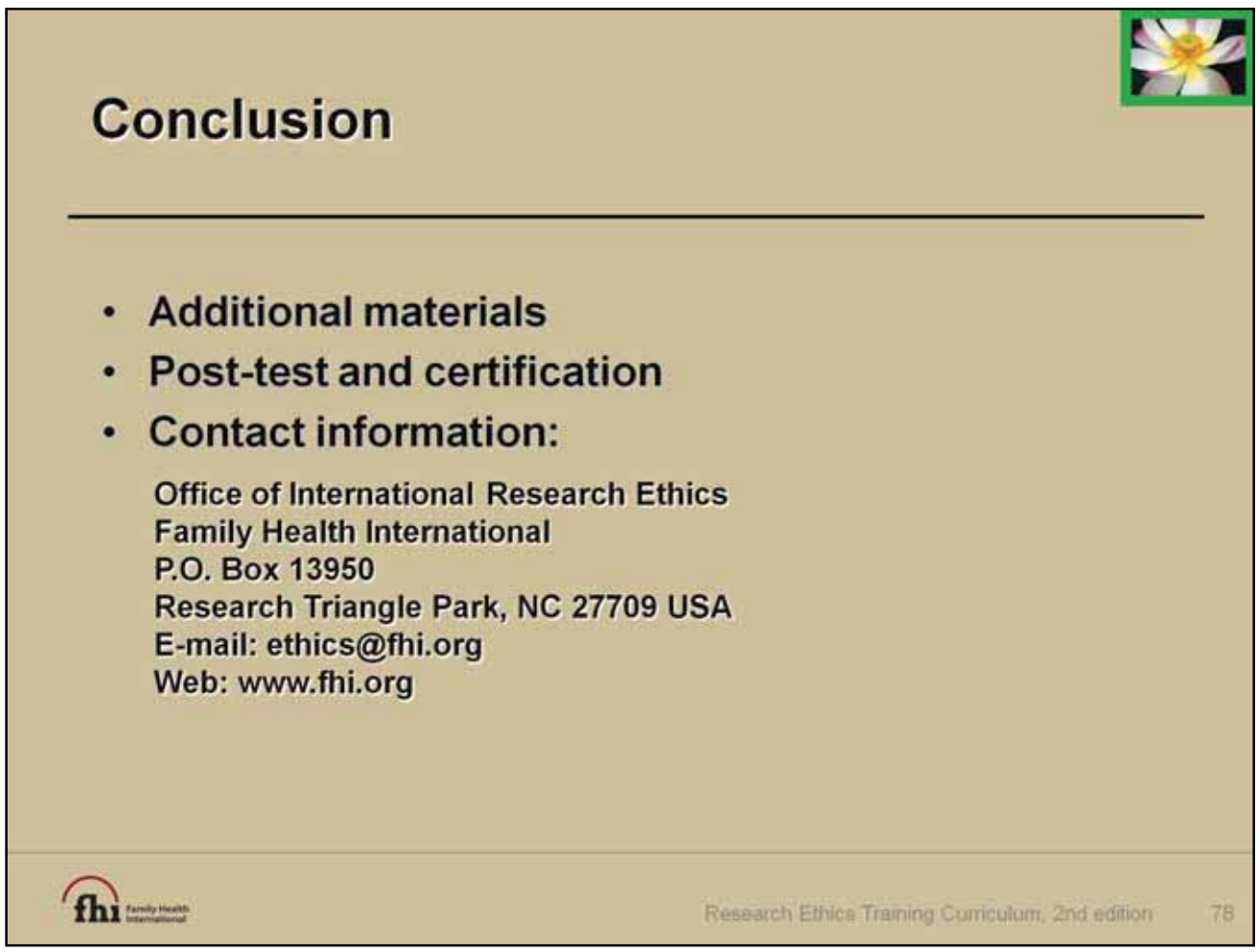


Case Study 4—Community Participation

Questions:

1. Can this injecting-drug user population (community) be included in this study? Why or why not?
2. What measures can the research staff take to ensure that informed consent is given freely by all participants?
3. If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?

Learner/Facilitator Note: At this point, the self-learner should review the case study, included in the *Case_Studies* section. The facilitator should have made copies of this case study to hand out to each of the group training participants. The Facilitator should also have carefully reviewed the instructions in the *Case Studies* section.



Conclusion

We hope that your interest in research ethics does not end with this curriculum. We encourage you to continue learning about research ethics and incorporating new elements in future studies.

Please go to the Evaluations section and take the necessary steps to obtain your certificate of completion as indicated under **Certificate of Completion** in the **Introduction** section of this curriculum.

Learner/Facilitator Note: Prepare a flip chart with the FHI contact information and your local contact information.

CASE STUDIES

Note to the Facilitator

The *Case Studies* section provides 10 health-research case studies to prompt discussion about the material presented in the curriculum.

Case Studies in the Curriculum

Case Study 1: Principles of Research Ethics (slide 13)
Case Study 2: Informed Consent (slide 46)
Case Study 3: Research Ethics Committee Considerations (slide 57)
Case Study 4: Community Participation (slide 77)

Additional Case Studies

Case Study 5: Inducement/Compensation
Case Study 6: Social Risks
Case Study 7: Respect for Persons
Case Study 8: Beneficence and Justice
Case Study 9: Individual versus Community Consent
Case Study 10: Research Involving Minors

The case studies are based on real-life research studies conducted throughout the world. They illustrate the complexity of human research and how cultural, social, and gender issues impact the ethics of a research study. The issues that are raised transcend any specific category of research and were selected to elicit a variety of reactions. This type of discussion will enrich the training group and should be pursued. The facilitator might find that discussion becomes so absorbing that he or she will need to curtail it in the interest of time.

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

Discussing the Case Studies

- The ideal way to discuss the case studies is to divide the participants into groups of eight and have them sit around group tables, round tables being preferred. Ask the groups to pretend to be formally established Research Ethics Committees.

- Each participant should receive a copy of the case study. Inform the participants that the discussions are to be based only on the information provided. Ask the groups to focus on ethical dilemmas rather than scientific design issues. Ask each group to designate a chairperson and a reporter.

- Allow five minutes for individual reading, followed by 15 minutes of group discussion. Have each reporter present the small-group findings to the entire group. Allow 20 to 25 minutes for discussion with the entire group.

- Each case study will take approximately 45 minutes. Adjust the number of case studies or groups presenting to fit into the time allowed for the entire workshop.

Resource for More Case Studies
The Research Policy and Cooperation Department of the World Health Organization published in 2009 the *Casebook on Ethical Issues in International Health Research.* The publication is available online at: http://www.who.int/rpc/research_ethics.

This casebook contains 63 case studies, each of which raises an important and difficult ethical issue connected with planning, reviewing, or conducting health-related research. The purpose of the book is to encourage thoughtful analysis of these issues by researchers and members of research ethics committees, particularly those involved with studies that are conducted or sponsored internationally. The case studies have been kept short and include only those descriptive, background details that are relevant to the case. Case studies in this publication were drawn from one or more actual research projects.

Readers and facilitators of this curriculum are encouraged to review the casebook as an alternative or addition to the case studies included in this curriculum.

Case Study 1. Principles of Research Ethics
Developing a Vaccine for Malaria

Source: *Casebook on Ethical Issues in International Health Research,* World Health Organization

A North American university is planning to test a multistage, DNA malaria vaccine. Preliminary studies in North America have been encouraging; immunization of human subjects shows evidence of a strong immune response. Experimental challenge studies in North American volunteers will begin soon. Larger field studies, both Phase II and III, are being planned. A country in sub-Saharan Africa where malaria is endemic has expressed interest in participating in the vaccine research effort. The African and North American researchers begin working together to design a study protocol to assess the vaccine's efficacy in reducing deaths due to malaria in children under five years of age, particularly infants.

A district in the country with a population of approximately 150,000 has developed an effective epidemiologic surveillance system. Trained community health workers (CHWs) visit all homes in each village in the district every three months to record all births, deaths, major illnesses, marriages, and migrations. A centralized, computerized record-keeping system was created and is regularly updated with data from the CHWs reports. Nevertheless, most of the villages are remote, and there are only four health posts to serve the entire population. Furthermore, in addition to the high malaria burden (18 percent of annual income lost due to the disease), trained health care workers, laboratory facilities, and medicines are in short supply. Children under five years of age in the study area suffer an average of six bouts of malaria a year. Fatally afflicted children and infants often die less than seventy-two hours after developing symptoms.

The researchers will randomly select potential participants (infants) for the vaccine trial from the database gathered by the CHWs. A study vaccination team will visit each home, explain the study, and obtain informed consent from the appropriate caregiver. Researchers will administer the vaccine or placebo in double-blind fashion to those who agree to participate. Although many children will experience some soreness at the injection site, the risks of vaccination are minor. Once all participants receive the vaccine, the team will leave the village without implementing any other interventions. Using the system already in place—that is, monitoring patients who come to the clinic or hospital with symptoms of malaria, as well as the active surveillance regularly conducted by the CHWs—researchers can collect data on subsequent illness and death due to malaria. If the vaccine is found to be effective, the benefit is prevention of morbidity or mortality due to malaria.

There is no clearly defined immunological marker to measure protective immunity against malaria. As mortality is the most important outcome variable that can be measured, the researchers will look at deaths as a study endpoint. To the extent that health records and verbal autopsies allow, the researchers are specifically interested in those deaths known to be caused by malaria. If all cases of malaria in the study

population were identified and treated, researchers could not measure the efficacy of the vaccine in preventing deaths. In the absence of a surrogate marker for mortality, the study researchers do not want to interfere with the “natural” consequences of malaria transmission in the study villages.

Questions

1. Is the use of a placebo appropriate in this context?
2. Is the study design appropriate to demonstrate the efficacy of the vaccine?
3. Should the researchers provide treatment for malaria cases in the community?
4. Should the researchers provide information on how to prevent illness?
5. The case study does not indicate that any provision has been made for an ethical review by the country where the research is being conducted. If the North American partners insist that the review conducted in North America is adequate, what should the host country do? If the host country does not have the capacity to provide ethical oversight, what options are available?

Case Study 2. Informed Consent
Development of a New Microbicide

Source: Family Health International

A randomized, placebo-controlled trial of a vaginal microbicide product is under way 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 Research Ethics Committee (REC) and sponsor's REC 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. 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 REC.

Question
In this case the REC should:
1. Recommend that the study be terminated (not allowed to continue).
2. Retrain the site investigator and the study staff in the informed consent process.
3. Rely on the site investigator's knowledge of the study population.
4. Take no action. Signed consent forms for each participant are on file.

Case Study 3. Research Ethics Committee Considerations
Testing a New Vaccine for Malaria

Source: Faculty of Health Sciences, University del Valle, Cali, Colombia

To test a human vaccine against malaria caused by *Plasmodium vivax*, a research group submits a three-phase protocol to the Research Ethics Committee (REC) of the local university. Differing from other protocols, a "challenge" methodology is proposed; researchers plan to infect research participants with malaria to evaluate the effectiveness of the vaccine the following way:

Phase Ia
The objective is to evaluate the model and the effectiveness of the infection (this model has not been implemented with *P. vivax* in any part of the world). Twenty-five volunteers will be exposed to five, four, or three bites in the left forearm by *Anopheles* mosquitoes infected with known and studied varieties of *P. vivax*. The participants will be monitored, and when they present malaria symptoms, they will be treated with conventional therapy.

Phase Ib
The objective is to correct possible problems occurring during the conduct of Phase Ia in 25 participants. The same methodology will be followed, with modifications made according to the results of the previous study.

Phase Ic
The objective is to establish the effectiveness of the vaccine. Two groups of 25 participants each will be established, with one group receiving the test vaccine and the other receiving a placebo. Both groups will be exposed to bites of the infected mosquitoes and will be followed for one year. If they present malaria symptoms, they will be evaluated and treated with conventional therapy.

The city where the study will be conducted does not have endemic malaria. Study participants will not be paid, as it is forbidden by national norms. However, they will be covered with insurance for standard medical care as available elsewhere in the country. Adverse events will be evaluated, and compensation for treatment, transportation, and missed working days will be provided as necessary.

When the REC asks researchers about alternatives to the proposed methodology, the research team mentions that this type of study has been conducted in rural, malaria-endemic sites with 300 volunteers receiving the vaccine and 300 volunteers receiving the placebo. The follow-up period was longer than that proposed for this study. The researchers justify the methodology because they feel they will have better control of the participants and will be able to provide better treatment in case of adverse events.

Questions
1. Is the study methodology appropriate?
2. Should the study be reviewed and approved phase by phase?

3. Are the protections for participants sufficient?
4. Should Phase Ib be eliminated?

Case Study 4. Community Participation
HIV Vaccine Study with At-Risk Groups

Source: Family Health International

An HIV vaccine trial is proposed in three large cities in Asia. The study will target previously identified at-risk groups, including injecting-drug users.

The research team plans to enroll injecting drug users at government-run rehabilitation centers and on the street. Most injecting-drug users in the rehabilitation centers have been sent there by the local legal system. Individuals who agree to participate in the research will receive an identification card with a participant number and contact information for questions or problems.

In preparation for the study, the researcher meets with rehabilitation center management and police staff to discuss the study and ask for their cooperation. The authorities who run the rehabilitation centers are optimistic that most of the injecting-drug users will agree to participate. In addition, the police request that participant identification cards include the police department's official seal and that the names of participants recruited on the street be provided to police so that they are not arrested and prevented access to the study. Community representatives are asked for input on the recruitment process.

Questions

1. Can this injecting-drug user population (community) be included in this study? Why or why not?
2. What measures can the research staff take to ensure that informed consent is given freely by all participants?
3. If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?

ADDITIONAL CASE STUDIES

Case Study 5. Inducement/Compensation
A Trial for Malaria Prophylaxis

Source: National Institute of Health Research and Development, Jakarta, Indonesia

A study in rural West Papua, Indonesia, is planned to determine the safety and prophylactic efficacy of Malarone for prevention of malaria among Indonesian transmigrants. The study will be placebo-controlled, randomized, and double-blinded in three phrases: I) a 17-day radical cure with Malarone; II) a 20-week administration of Malarone versus placebo; and III) a four-week post-prophylaxis follow-up, for a total duration of 27 weeks. Participants will be transmigrants who are at least 12 years old and have been residents of West Papua for three to 20 months.

Four hundred subjects are expected to successfully complete Phase I of the study. Volunteers will be randomized to continue or discontinue the trial after Phase I. Those randomized to continue will be further randomized to receive either Malarone or placebo. Those randomized to discontinue will be asked to enroll in an open-label study of pimaquine as a prophylactic. Malaria smears will be done at screening, at the end of the radical cure, once weekly during Phase II, and at any time that malaria-like illness develops.

As medications should be taken with food, both will be provided free of charge to participants. There will be 24-hour coverage by an on-site physician and transportation to the Jayapura General Hospital in case of emergencies. A medical monitor will assure patient well-being and compliance with all safeguards as described in the protocol.

If a participant develops malaria during the prophylaxis phase of the study, he or she will be treated with a three-day course of Malarone. If a participant develops a complication during any phase, he or she will receive prompt medical care free of charge (including transportation to and the costs of hospitalization in Jayapura, if referral is medically indicated according to the local standard of care). Prompt diagnosis, treatment, and follow-up will be provided to volunteers for non-malarial illnesses or injuries that develop during their participation in the study.

Questions

1. Is there undue inducement in the study?
2. Is the use of placebo justified?
3. Are the safeguards adequate?
4. Do the benefits justify the study?
5. What information should be provided to participants before enrollment?
6. Is the selection of the study site at a transmigrant settlement appropriate?

Case Study 6. Social Risks
Comparison of Female and Male Condoms

Source: Family Health International

A cluster-randomized trial is being 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, 1 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 their 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 researchers at both intervention and control sites. This is the only problem reported in the research study thus far.

Question
How should the REC advise the researchers?

1. Stop the research to protect the women.
2. Amend the informed consent form and re-consent all participants.
3. Continue the study, but orally inform participants of the risks.
4. Continue the study as designed.
5. Add messages about domestic violence to the intervention and report the violent episodes to management at the plantations.

Case Study 7. Respect for Persons
Sexually Transmitted Infections among Commercial Sex Workers

Source: Family Health International

A 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 three common STIs and will participate in an interview. Participants will receive a card with a number linking them to their blood sample and will have the option of presenting their cards to get the results of the STI tests. Those with positive results for any of the three 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, a 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 researchers take to ensure that 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 8. Beneficence and Justice
Study on Condom Use

Source: Family Health International

A time-series intervention trial is being conducted with commercial sex workers. The goal of the trial is 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 is estimated by interviewing study participants about their use of protection in their last 10 sex acts. These measurements are to be made at five points: twice following exposure to promotion and distribution activities for the male condom, and three times following exposure to promotion and distribution of both the male and female condom.

The local principal investigator, a highly respected advocate for the sex workers, explains that women are 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 percent 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 effect 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?
1. Continue the study as designed.
2. Terminate the study at this point.
3. Suspend the study. Seek assurance that female condoms will be made available if proved successful.

Case Study 9. Individual versus Community Consent
The Impact of Vitamin A on Diarrhea in Children

Source: Harvard School of Public Health, USA

A U.S. university gives a grant to conduct a study to evaluate the impact of periodic doses of high-dose vitamin A on the incidence of diarrhea and acute respiratory infection (ARI) in children less than five years of age.

High-dose vitamin A capsules or placebo would be administered in a double-blind fashion every four months for one year to children from six months to five years of age. A record of morbidity (diarrhea and ARI) and mortality data would be measured weekly, and blood samples for vitamin A status would be drawn at zero, six, and 12 months.

To inform the community of the impending study, the local chief and council of elders called the villagers together. In a festive environment, the researchers described the study and answered questions from community members and the council. Later, the village chief and council met briefly and gave their approval.

Shortly thereafter, in accordance with the guidelines of the funding university's Institutional Review Board* (IRB), the field staff began going house to house to obtain signed parental informed consent for children to participate in the study. The mothers (usually the parent at home during the visit) said that they did not need to sign anything as the chief had already approved the study and they could not sign anything because they could not read what they would be signing. On the second day, the field staff were summoned to the chief's house and politely informed that since the chief and council had given approval for the study, it was both unnecessary and unacceptable to seek individual signatures. The staff said the grant agreement required them to obtain signed informed consent forms. They were told that if they insisted on doing so, they would have to leave the community.

Questions

1. How should the reseacher handle this problem?
2. How critical is signed informed consent in this setting?
3. Is it acceptable to obtain consent from the village chief or is individual consent necessary?
4. Is informed consent culturally bound or is it a universal principle?
5. Are there circumstances when informed consent is unnecessary?
6. Does it protect the researcher or the participant?
7. Can the IRB waive informed consent in such instances?

* In this curriculum, Institutional Review Boards are referred to as Research Ethics Committees (RECs). The authors have preserved the terminology used by the contributing institute.

Case Study 10. Research Involving Minors
Comparing Childhood Vaccination Regimens

Source: El Salvador National Ethics Committee, San Salvador, El Salvador

A study is being planned to compare a new childhood vaccine consisting of five components in a single dose with the existing regimen. At present, children in this country receive a vaccine with three components in a single dose, and two additional components in a separate dose, all given during the same visit.

The study group will be boys and girls, 15 months old, who would go to the country's Health Units for the current vaccination regimen. The plan is to enroll 300 children in three months. After parental informed consent, children will be randomized to receive the current vaccination regimen or the new, one-dose regimen.

The investigation would be conducted in five Health Units of the Ministry of Health, where the application of the current vaccination regimen is mandatory and free of charge. The Ministry of Health has given approval to conduct the study.

The main endpoints are:
- Adverse experiences or reactions to the vaccine.
- Antibodies produced in response to the vaccines. For this purpose, the children will have to provide a blood sample at the time of the injection and one month after.

Blood samples will be taken at each clinic, be sent to a central laboratory, and then be sent out of country for antibody analysis. Private pediatricians will be contracted as investigators to reinforce the pediatricians of the Health Units. In case of adverse events, participants would be referred to the government's Children's Hospital.

Observations:
- The parents of children seeking care in the Health Units typically are economically poor.
- Most of the parents do not read and write and have little formal education.
- Children often come to the Health Units with individuals other than parents, who are often working.

Questions
1. Should the sponsor of the study provide the Ministry of Health with the control treatment as well as the study product?
2. Should the study be conducted only in the Health Units and not in private clinics?
3. Is the enrollment plan, to be conducted in very busy clinics, realistic? Will there be enough time to explain and obtain informed consent?
4. Can researchers assure that the individuals accompanying the children have legal responsibility for the child? What should researchers do in cases where legal responsibility is uncertain?

5. Can researchers assure that parents will allow the children to provide blood samples? Can researchers assure that the children return to the clinic for follow-up blood sampling or adverse events?
6. How should researchers ensure the control of the blood samples during transport to the central laboratory and out of the country?
7. Should children with adverse events be referred to the Ministry of Health hospital or a private hospital?

CASE STUDIES—DISCUSSION POINTS

Case Study 1. Principles of Research Ethics
Developing a Vaccine for Malaria

1. **Is the use of a placebo appropriate in this context?**
   The Declaration of Helsinki recommends "that a new intervention must be tested against the best current proven intervention." In this case, if evidence is presented that such an intervention does not exist, the use of a placebo would be justified. CIOMS recommends that "ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design." If this were a non-IND study considered for submission to the U.S. Food and Drug Administration (FDA) as support for an IND, current FDA regulations would require the study to be conducted in accordance with GCP rather than the Declaration of Helsinki.

2. **Is the study design appropriate to demonstrate the efficacy of the vaccine?**
   The study design raises several ethical and scientific issues. The statement: "Once all participants receive the vaccine, the team will leave the village without implementing any other interventions," indicates that the team will leave without further consideration for the protection of the participants. Also, mortality as the endpoint of efficacy could be debated by REC members with expertise in this type of research. In complex studies such as this one, the use of special scientific consultants to assist the REC might be considered.

3. **Should the researchers provide treatment for malaria cases in the community?**
   The reviewing REC must carefully assess the level of access research participants have to appropriate health care and whether there is a need to provide malaria treatment for all research participants. If it is decided that treatment will be provided, the design of the study would require major changes, which would have important cost implications, such as changes in the required sample size.

4. **Should the researchers provide information on how to prevent illness?**
   The need to provide prevention information requires careful assessment by the REC. The REC should consider the current standard for malaria prevention as a reference. As in the case of treatment, a requirement for prevention information would incur major changes to the study. However, the provision of prevention has been required in comparable studies. The extension of these two benefits (treatment and prevention information) to the entire community, though desirable, is not the direct responsibility of the research study.

5. **The case study does not indicate that any provision has been made for an ethical review by the country where the research is being conducted. If the North American partners insist that the review conducted in North America is adequate, what should the host country do? If the host country does not have the capacity to provide ethical oversight, what options are available?**
   The review and approval of the research project by an REC in the country where the

research is conducted must be required. CIOMS specifically recommends that the "U.S. government should not sponsor clinical trials in developing countries unless such trials have received prior approval by an ethics committee in the host country and by a U.S. Institutional Review Board." The absence of local capacity to provide ethical oversight must be documented clearly. In the proven absence of local capacity, the reviewing REC should require, review, and approve the local mechanisms of ethical oversight that will be set in place.

Case Study 2. Informed Consent
Development of a New Microbicide

In this case the REC should:

1. **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.

2. **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.

3. **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 might 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.

4. **No action. Signed consent forms for each participant are on file.**
   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 3. Research Ethics Committee Considerations
Testing a New Vaccine for Malaria

1. **Is the study methodology appropriate?**
   The development of a new drug or vaccine goes through sequential and progressive phases to ensure the safe development of a new product. Preclinical studies are conducted in basic science laboratories and in animals appropriate for the product under study. These studies are designed to provide preliminary information on the safety and efficacy of the product prior to experimentation in humans. The data obtained at the preclinical level are then submitted to a regulatory agency (e.g., U.S. Food and Drug Administration) to obtain permission to initiate studies in humans (clinical trials).

   In addition to the REC approval, the initiation of a study as proposed would also require permission by the national regulatory agency and the regulatory agency in the country of origin of the vaccine.

   A challenge study is justified only when the scientific rationale for the study is very clear, the information gained is very important for an outlined development process, appropriate protections for participants are in place, and the study will be conducted by highly experienced investigators in sites with high-quality health care facilities.

2. **Should the study be reviewed and approved phase by phase?**
   Approving study continuation phase by phase, through progress reports, is an acceptable option. In reality, Phase Ic would only be a first, relatively minor step to establish the effectiveness of the vaccine. This study would have to be followed by a number of large and expensive studies. The REC should be informed of the entire plan for the development of the vaccine as a consideration for its approval of the study.

3. **Are the protections for participants sufficient?**
   The assurance that appropriate protections will be provided to the study participants is most important. The informed consent should provide clear and comprehensible information on the study design and its risks and benefits. Rapid access to high-quality care must be confirmed, including possible long-term care for complications related to study participation.

4. **Should Phase Ib be eliminated?**
   The elimination of Phase Ib is a valid consideration. This decision requires important scientific expertise in the area, which might exist within the REC or be obtained through expert advisors.

The reasons for approval given by the local REC were:

- The number of study participants is smaller, which means a lower risk of a serious adverse event for the study population.

- Recruitment in a city allows the researchers to enroll participants with a better understanding of the research and avoids coercion of volunteers from endemic areas.
- The follow-up and staff capacity are better in the city than in a rural, endemic area where health resources, communication, and ability to transfer participants for further care may be limited.
- It allows for open recruitment, with better social vigilance, due to the presence of good communication and the local REC.

Case Study 4. Community Participation
HIV Vaccine Study with At-Risk Groups

1. **Can this injecting-drug user population (community) be included in this study? Why or why not?**
   It might be possible to include these injecting-drug users, but only with a well-designed informed consent process that includes multiple, advanced meetings with the authorities to ensure that they understand the nature of the study and to reiterate that participation is voluntary. The study should stress that it is acceptable to have a large number of this community refuse participation.

2. **What measures can the research staff take to ensure that informed consent is given freely by all participants?**
   It will be essential to use a private room for informed consent discussions. Members of the rehabilitation center staff should not be present for the discussions. Participation in the study should not result in an award or favorable treatment of rehabilitation center detainees. Also, informing the injecting-drug user community of the research in advance might mean that some of the detainees are aware of the research before they are sent to the rehabilitation centers.

3. **If you believe that the potential participants will not be able to give voluntary informed consent, what could be done to change the informed consent process?**
   If you believe that they will not be able to give voluntary informed consent, they should not be enrolled. It might be better to recruit only injecting-drug users who are not detained in rehabilitation centers.

Case Study 5. Inducement/Compensation
A Trial for Malaria Prophylaxis

1. **Is there undue inducement in the study?**
   As indicated in the protocol, one of the main objectives of the study was to determine the safety and efficacy of malaria prevention among Indonesian transmigrants. Particular social and economic situations might apply to this population, and it might be considered a vulnerable population requiring special protections.

2. **Is the use of placebo justified?**
   The Declaration of Helsinki states: "the use of placebo or no treatment is acceptable where no current proven intervention exists." The reviewing REC should request documentation from the research team that no current proven intervention exists. Otherwise, the use of Malarone should be tested against the best current proven alternative. The REC may allow placebo use if compelling scientific reasons are presented and there is no risk of serious harm. As in Case Study 1, if this were a non-IND study considered for submission to the U.S. Food and Drug Administration (FDA) as support for an IND, current FDA regulations would require the study to be conducted in accordance with GCP rather than the Declaration of Helsinki.

3. **Are the safeguards adequate?**
   In addition to the described safeguards, consideration should be given to provide the standard of malaria prevention (other than drugs) to all participants.

4. **Do the benefits justify the study?**
   In general, the benefit-risk analysis justifies the study. Provision of the standard of malaria prevention should be considered.

5. **What information should be provided to participants before enrollment?**
   Information on the meaning of placebo-controlled study should be made very understandable to the participants. It must be very clear to them that some of them will not receive any treatment.

6. **Is the selection of the study site at a transmigrant settlement appropriate?**
   There is no apparent undue influence in the study. The level of health care provided is appropriate for the participants' protection.

Case Study 6. Social Risks
Comparison of Female and Male Condoms

How should the REC advise the researchers?

1. **Stop the research to protect the women.**
   While this is certainly an option, it is an extreme one. It might be worthwhile to look for a way to continue the study and reduce the possibility of violence.

2. **Amend the informed consent form and re-consent 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 might decide to not participate.

3. **Continue the study, but orally inform participants of the risks.**
   A good answer, but others might be better. Implementing this change would take less time than repeating the written consent process, but the quality of the information might be degraded.

4. **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.

5. **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 might cause more violent outbursts. However, it might be advisable to amend the intervention to include information about domestic violence.

Case Study 7. Respect for Persons
Sexually Transmitted Infections among Commercial Sex Workers

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 might 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.

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 might 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.)

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 might not face pressure from a manager that would alter their decision.

Case Study 8. Beneficence and Justice
Study on Condom Use

What is the best way to proceed?

1. **Continue the study as designed.**
   While this is certainly an option, continuing the study might not be in the best interest of the participants. The established high rate of male condom use and the uncertain poststudy availability of the female condom make this a poor choice.

2. **Terminate the study at this point.**
   This is the **best answer**. The study might have scientific merit, but this is clearly not the best participant population.

3. **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 9. Individual versus Community Consent
The Impact of Vitamin A on Diarrhea in Children

In principle, this potential problem could have been identified in the development phase of the research project. As indicated in the *Informed Consent* section of this curriculum, the informed consent process begins before the study initiation. At this stage, the investigating team gains knowledge of the local culture and social norms, and the informed process is designed accordingly.

1. **How should the reseacher handle this problem?**
   The field investigator should maintain open and collegial communication with the village chief and the university's Institutional Review Board. His or her goal is to initiate the study with both sides in agreement. The Nuffield Council on Bioethics document, *The Ethics of Research Related to Healthcare in Developing Countries*, indicates that local practices must be respected, even if they complicate the research.

2. **How critical is signed informed consent in this setting?**
   It is important to distinguish between the waiving of the requirement to obtain informed consent and the waiving of the requirement to obtain a signed informed consent form. A signed informed consent in this setting does not seem to be necessary.

3. **Is it acceptable to obtain consent from the village chief or is individual consent necessary?**
   CIOMS international ethics guidelines (2002) read: "In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual consent."

4. **Is informed consent culturally bound or is it a universal principle?**
   Informed consent is a universal principle for research involving human participants. However, how the informed process is designed and how the information is presented and documented are culturally bound.

5. **Are there circumstances when informed consent is unnecessary?**
   Yes, there are circumstances, clearly delineated in national regulations, when the requirement for informed consent or its signed documentation may be waived by the responsible REC. A useful reference is the U.S. Code of Federal Regulations, included in the *Additional Resources* section of this curriculum.

6. **Does it protect the researcher or the participant?**
   The basic purpose of informed consent is to protect the research participant. It might also provide some legal protection to the investigator, but this is not its main purpose.

7. **Can the REC waive informed consent in such instances?**
   As indicated in the answer to Question 5, an REC may waive informed consent. Preferably, the waiver should be made by the local reviewing REC.

Case Study 10. Research Involving Minors
Comparing Childhood Vaccination Regimens

Research involving minors, considered a vulnerable population, requires special REC attention. The major national and international regulations include special sections on protections for children. These regulations include assuring that research does not involve greater than minimal risk and requiring permission by parents or guardians. It is essential for a REC to have access to local or national regulations on the subject. One essential REC determination is whether this study involves minimal risk or a greater than minimal risk, and the prospect of direct benefit to the participants. One point to consider might be whether the risk of applying the five components in one single injection is comparable to the risk of applying the same five components in two injections in the same visit.

1. **Should the sponsor of the study provide the Ministry of Health with the control treatment as well as the study product?**
   The study is presented as a comparison of the currently available vaccine provided by the Ministry of Health (MOH) with a new vaccine provided by the sponsor. Whether the sponsor should pay the MOH for the currently used vaccine is a valid consideration. But it could also be a contribution of the MOH.

2. **Should the study be conducted only in the Health Units and not in private clinics?**
   The population selected for the study is children attending government Health Units, not children attending private clinics. This is what the REC is being asked to review.

3. **Is the enrollment plan, to be conducted in very busy clinics, realistic? Will there be enough time to explain and obtain informed consent?**
4. **Can researchers assure that the individuals accompanying the children have legal responsibility for the child? What should researchers do in cases where legal responsibility is uncertain?**
5. **Can researchers assure that parents will allow the children to provide blood samples? Can researchers assure that the children return to the clinic for follow-up blood sampling or adverse events?**
6. **How should researchers ensure the control of the blood samples during transport to the central laboratory and out of the country?**

   Questions 3 to 6 are valid questions, and the REC might rightfully demand a satisfactory response to approve the study. They address mostly administrative procedures related to the study. The investigator should be given the opportunity to address these questions. The presence of the investigator at the time of REC discussions is a practical option. However, the investigator should not be present at the time of deliberation.

7. **Should children with adverse events be referred to the Ministry of Health hospital or a private hospital?**
   This question seems to indicate a concern that the quality of health care might be better at a private hospital than at the government hospitals. The REC should require

the same high-quality level of health care at either site. As in Question 1, whether the sponsor should pay for health care costs at the government hospital is a valid consideration.

Research Ethics Training Curriculum

Second Edition

Additional Resources

Title 45: Public Welfare

PART 46—PROTECTION OF HUMAN SUBJECTS

Section Contents

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

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

Subpart E—Registration of Institutional Review Boards

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

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 demonstration 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

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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?

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(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate 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 procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported 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 conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities 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 settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation 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 subjects' 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 educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation 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 statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

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

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or 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.

(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 environmental 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 Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain 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 conducted, 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 requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(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 provide 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 procedures prescribed by the institution afford 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 procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in theFederal Registeror will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in theFederal Registeror in such other manner as provided in department or agency procedures.[1]

[1] Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A–D. Some of the other Departments and Agencies have incorporated 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, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation 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 participate in the activities being observed.

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.102 Definitions.

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(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, 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 prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research 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 regulation,* and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

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

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(a) Each institution engaged in research 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 requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, 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 assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office.

(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 provided 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 governing 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 regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment 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 membership shall be reported to the department or agency head, unless in accord with §46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Human Research Protections, HHS, or any successor office.

(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 require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval 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, appropriate 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 determinations of the IRB and (ii) any suspension or termination of IRB approval.

(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 imposed by this policy and shall be filed in such form and manner as the department 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 department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial 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 during which any particular approved assurance 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 department or agency and not otherwise exempted or waived under §46.101 (b) or (i). An institution with an approved assurance shall certify that each application 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 proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under Control Number 0990–0260)

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§§ 46.104-46.106 [Reserved]

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§ 46.107 IRB membership.

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(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted 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 community attitudes, to promote respect for its advice and counsel in safeguarding 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 acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced 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 consideration 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 affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite 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.

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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 meetings at which a majority of the members 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 majority of those members present at the meeting.

§ 46.109 IRB review of research.

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(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation 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 decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification 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 policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

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(a) The Secretary, HHS, has established, and published as a Notice in theFederal 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 theFederal Register. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved 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 experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance 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 research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.111 Criteria for IRB approval of research.

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(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic 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 distinguished 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 involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

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

(5) Informed consent will be appropriately 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 ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality 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 included in the study to protect the rights and welfare of these subjects.

§ 46.112 Review by institution.

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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 officials may not approve the research if it has not been approved by an IRB.

§ 46.113 Suspension or termination of IRB approval of research.

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An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons 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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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.114 Cooperative research.

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Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible 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 avoiding duplication of effort.

§ 46.115 IRB records.

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(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

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

(3) Records of continuing review activities.

(4) Copies of all correspondence between 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 required by §46.116(b)(5).

(b) The records required by this policy 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 accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

(Approved by the Office of Management and Budget under Control Number 0990–0260)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.116 General requirements for informed consent.

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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 investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative 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 institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(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 reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, 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 explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; 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 participation 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 information 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 become 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 consent;

(3) Any additional costs to the subject 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 participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain 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 government 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 practicably 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 elements 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 practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally 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 0990–0260)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.117 Documentation of informed consent.

top

(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 representative. A copy shall be given to the person 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 subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject 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 representative. 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 requirement 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 subject wants documentation linking the subject with the research, and the subject'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 required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(Approved by the Office of Management and Budget under Control Number 0990–0260)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§ 46.118 Applications and proposals lacking definite plans for involvement of human subjects.

top

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

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

top

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§ 46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

top

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits 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]

top

§ 46.122 Use of Federal funds.

top

Federal funds administered by a department or agency may not be expended 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.

top

(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 supporting or approving applications or proposals covered by this policy the department 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 termination or suspension under paragarph (a) of this section and whether the applicant 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, materially 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.

top

With respect to any research project or any class of research projects the department 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 additional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

top

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§ 46.201 To what do these regulations apply?

top

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

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

§ 46.202 Definitions.

top

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in theFederal Registerguidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§ 46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

top

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 applicable sections of this subpart and the other subparts of this part.

§ 46.204 Research involving pregnant women or fetuses.

top

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit,

the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§ 46.205 Research involving neonates.

top

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions are met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§ 46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

top

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§ 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

top

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §§46.204 or 46.205 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in theFederal Register,has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

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

top

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

§ 46.301 Applicability.

top

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving 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.

top

Inasmuch as prisoners may be under constraints because of their incarceration 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 protection of prisoners involved in activities to which this subpart is applicable.

§ 46.303 Definitions.

top

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

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

(c) *Prisoner* means any individual involuntarily 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 arraignment, 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 medical, dental, or psychological examination of healthy persons.

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

top

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive 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 representative with appropriate background and experience to serve in that capacity, except that where a particular 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 Institutional Review Boards where prisoners are involved.

top

(a) In addition to all other responsibilities 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 represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities 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 impaired;

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

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification 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 particular 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 account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed 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' sentences, 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 manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§ 46.306 Permitted research involving prisoners.

top

(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 research 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, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in theFederal Register,of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving 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 approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in theFederal Register,of his intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

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

top

Source: 48 FR 9818, Mar. 8, 1983, unless otherwise noted.

§ 46.401 To what do these regulations apply?

top

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department 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 nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted 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 Subpart A, waive the applicability of some or all of the requirements of these regulations 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. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research 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 subpart.

[48 FR 9818, Mar. 8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991]

§ 46.402 Definitions.

top

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(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 research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent(s) or guardian to the participation 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.

top

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 applicable sections of this subpart.

§ 46.404 Research not involving greater than minimal risk.

top

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, 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.

top

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 monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable 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 subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

top

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 increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition 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 guardians, as set forth in §46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

top

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 affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following 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 understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(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 assent by children.

top

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children,

when in the judgment of the IRB the children are capable of providing 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 involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines 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 involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context 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 subjects 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 sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission 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 sufficient 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 parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably 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 research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart 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 inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

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

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§ 46.409 Wards.

top

(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, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition 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 research 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 organization.

Subpart E—Registration of Institutional Review Boards

top

Source: 74 FR 2405, Jan. 15, 2009, unless otherwise noted.

§ 46.501 What IRBs must be registered?

top

Each IRB that is designated by an institution under an assurance of compliance approved for federalwide use by the Office for Human Research Protections (OHRP) under §46.103(a) and that reviews research involving human subjects conducted or supported by the Department of Health and Human Services (HHS) must be registered with HHS. An individual authorized to act on behalf of the institution or organization operating the IRB must submit the registration information.

§ 46.502 What information must be provided when registering an IRB?

top

The following information must be provided to HHS when registering an IRB:

(a) The name, mailing address, and street address (if different from the mailing address) of the institution or organization operating the IRB(s); and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer or head official of that institution or organization who is responsible for overseeing activities performed by the IRB.

(b) The name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(c) The name, if any, assigned to the IRB by the institution or organization, and the IRB's mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address.

(d) The name, phone number, and electronic mail address of the IRB chairperson.

(e)(1) The approximate numbers of:

(i) All active protocols; and

(ii) Active protocols conducted or supported by HHS.

(2) For purpose of this regulation, an “active protocol” is any protocol for which the IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding twelve months.

(f) The approximate number of full-time equivalent positions devoted to the IRB's administrative activities.

§ 46.503 When must an IRB be registered?

top

An IRB must be registered before it can be designated under an assurance approved for federalwide use by OHRP under §46.103(a). IRB registration becomes effective when reviewed and accepted by OHRP. The registration will be effective for 3 years.

§ 46.504 How must an IRB be registered?

top

Each IRB must be registered electronically through *http://ohrp.cit.nih.gov/efile* unless an institution or organization lacks the ability to register its IRB(s) electronically. If an institution or organization lacks the ability to register an IRB electronically, it must send its IRB registration information in writing to OHRP.

§ 46.505 When must IRB registration information be renewed or updated?

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(a) Each IRB must renew its registration every 3 years.

(b) The registration information for an IRB must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information or the IRB chairperson. The updated registration information must be submitted in accordance with §46.504.

(c) Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.

(d) An institution's or organization's decision to disband a registered IRB which it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB's review of HHS-conducted or -supported research.

THE NUREMBERG CODE

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Of the ten principles which have been enumerated our judicial concern, of course, is with those requirements which are purely legal in nature — or which at least are so clearly related to matters legal that they assist us in determining criminal culpability and punishment. To go beyond that point would lead us into a field that would be beyond our sphere of competence. However, the point need not be labored. We find from the evidence that in the medical experiments which have been proved, these ten principles were much more frequently honored in their breach than in their observance. Many of the concentration camp inmates who were the victims of these atrocities were citizens of countries other than the German Reich. They were non-German nationals, including Jews and "asocial persons", both prisoners of war and civilians, who had been imprisoned and forced to submit to these tortures and barbarities without so much as a semblance of trial. In every single instance appearing in the record, subjects were used who did not consent to the experiments; indeed, as to some of the experiments, it is not even contended by the defendants that the subjects occupied the status of volunteers. In no case was the experimental subject at liberty of his own free choice to withdraw from any experiment. In many cases experiments were performed by unqualified persons; were conducted at random for no adequate scientific reason, and under revolting physical conditions. All of the experiments were conducted with unnecessary suffering and injury and but very little, if any, precautions were taken to protect or safeguard the human subjects from the possibilities of injury, disability, or death. In every one of the experiments the subjects experienced extreme pain or torture, and in most of them they suffered permanent injury, mutilation, or death, either as a direct result of the experiments or because of lack of adequate follow-up care.

Obviously all of these experiments involving brutalities, tortures, disabling injury, and death were performed in complete disregard of international conventions, the laws and customs of war, the general principles of criminal law as derived from the criminal laws of all civilized nations, and Control Council Law No. 10. Manifestly human experiments under such conditions are contrary to "the principles of the law of nations as they result from the usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience."

Whether any of the defendants in the dock are guilty of these atrocities is, of course, another question Under the Anglo-Saxon system of jurisprudence every defendant in a criminal case is presumed to be innocent of an offense charged until the prosecution, by competent, credible proof, has shown his guilt to the exclusion of every reasonable doubt. And this presumption abides with the defendant through each stage of his trial until such degree of proof has been adduced. A "reasonable doubt" as the name implies is one conformable to reason — a doubt which a reasonable man would entertain. Stated differently, it is that state of a case which, after a full and complete comparison and consideration of all the evidence, would leave an unbiased,

unprejudiced, reflective person, charged with the responsibility for decision, in the state of mind that he could not say that he felt an abiding conviction amounting to a moral certainty of the truth of the charge.

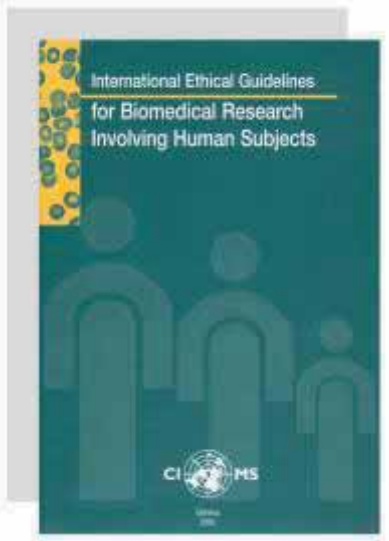
If any of the defendants are to be found guilty under counts two or three of the indictment it must be because the evidence has shown beyond a reasonable doubt that such defendant, without regard to nationality or the capacity in which he acted, participated as a principal in, accessory to, ordered, abetted, took a consenting part in, or was connected with plans or enterprises involving the commission of at least some of the medical experiments and other atrocities which are the subject matter of these counts. Under no other circumstances may he be convicted.

Before examining the evidence to which we must look in order to determine individual culpability, a brief statement concerning some of the official agencies of the German Government and Nazi Party which will be referred to in this judgment seems desirable.

Source
THE NUREMBERG CODE [from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Nuremberg, October 1946–April 1949. Washington, D.C.: U.S. G.P.O, 1949–1953.]

Council for International Organizations of Medical Sciences (CIOMS)

International Ethical Guidelines for Biomedical Research Involving Human Subjects



The Council for International Organizations of Medical Sciences (CIOMS) announces the publication of its revised/updated *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

This 2002 text supersedes the 1993 Guidelines. It is the third in the series of biomedical-research ethical guidelines issued by CIOMS since 1982. Its core consists of 21 guidelines with commentaries. A prefatory section outlines the historical background and the revision process, and includes an introduction, an account of earlier instruments and guidelines, a statement of ethical principles and a preamble. An Appendix lists the items to be included in the research protocol to be submitted for scientific and ethical review and clearance. Appendices include also the World Medical Association's Declaration of Helsinki.

The Guidelines relate mainly to *ethical justification and scientific validity of research; ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health-care services.*

Their scope reflects the changes, the advances and the controversies that have characterized biomedical research ethics in the last two decades. Like those of 1982 and 1993, the 2002 CIOMS Guidelines are designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms. A particular aim is to reflect the conditions and the needs of low-resource countries, and the implications for multinational or transnational research in which they may be partners.

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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)

CIOMS
Geneva
2002

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Vulnerable groups

Women as research participants

* * * * *

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences (CIOMS) acknowledges the substantial financial contribution of the Joint United Nations Programme on HIV/AIDS (UNAIDS) to the preparation of the 2002 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. The World Health Organization in Geneva contributed generously also through the departments of Reproductive Health and Research, Essential Drugs and Medicines Policy, Vaccines and Biologicals, and HIV/AIDS/Sexually Transmitted Infections, as well as the Special Programme for Research and Training in Tropical Diseases. CIOMS was at all times free to avail of the services and facilities of WHO.

CIOMS acknowledges also with much appreciation the financial support to the project from the Government of Finland, the Government of Switzerland, the Swiss Academy of Medical Sciences, the Fogarty International Center at the National Institutes of Health, USA, and the Medical Research Council of the United Kingdom.

A number of institutions and organizations made valuable contributions by making their experts available at no cost to CIOMS for the three meetings held in relation to the revision project. This has been highly appreciated.

The task of finalizing the various drafts was in the hands of Professor Robert J. Levine, who served as consultant to the project and chair of the steering committee, and whose profound knowledge and understanding of the field is remarkable. He was ably assisted by Dr James Gallagher of the CIOMS

secretariat, who managed the electronic discussion and endeavoured to accommodate or reflect in the text the numerous comments received. He also edited the final text. Special mention must be made of the informal drafting group set up to bring the influence of various cultures to bear on the process. The group, with two members of the CIOMS secretariat, met for five days in New York in January 2001 and continued for several months to interact electronically with one another and with the secretariat to prepare the third draft, posted on the CIOMS website in June 2001: Fernando Lolas Stepke (chair), John Bryant, Leonardo de Castro, Robert Levine, Ruth Macklin, and Godfrey Tangwa; the group continued from October 2001, together with Florencia Luna and Rodolfo Saracci, to cooperate in preparing the fourth draft. The contribution of this group was invaluable.

The interest and comments of the many organizations and individuals who responded to the several drafts of the guidelines posted on the CIOMS website or otherwise made available are gratefully acknowledged (Appendix 6)

At CIOMS, Sev Fluss was at all times ready and resourceful when consulted, with advice and constructive comment, and Mrs Kathryn Chalaby-Amsler responded most competently to the sometimes considerable demands made on her administrative and secretarial skills.

BACKGROUND

The Council for International Organizations of Medical Sciences (CIOMS) is an international nongovernmental organization in official relations with the World Health Organization (WHO). It was founded under the auspices of WHO and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949 with among its mandates that of maintaining collaborative relations with the United Nations and its specialized agencies, particularly with UNESCO and WHO.

CIOMS, in association with WHO, undertook its work on ethics in relation to biomedical research in the late 1970s. At that time, newly independent WHO Member States were setting up health-care systems. WHO was not then in a position to promote ethics as an aspect of health care or research. It was thus that CIOMS set out, in cooperation with WHO, to prepare guidelines " to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements". The World Medical Association had issued the original Declaration of Helsinki in 1964 and an amended version in 1975. The outcome of the CIOMS/WHO undertaking was, in 1982, *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

The period that followed saw the outbreak of the HIV/AIDS pandemic and proposals to undertake large-scale trials of vaccine and treatment drugs for the condition. These raised new ethical issues that had not been considered in the preparation of *Proposed Guidelines*. There were other factors also – rapid advances in medicine and biotechnology, changing research practices such as multinational field trials, experimentation involving vulnerable population groups, and also a changing view, in rich and poor countries, that research involving human subjects was largely beneficial and not threatening. The Declaration of Helsinki was revised twice in the 1980s – in 1983 and 1989. It was timely to revise and update the 1982 guidelines, and CIOMS, with the cooperation of WHO and its Global Programme on AIDS, undertook the task. The outcome was the issuing of two sets of guidelines: in 1991, *International Guidelines for Ethical Review of Epidemiological Studies*; and, in 1993, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

After 1993, ethical issues arose for which the CIOMS Guidelines had no specific provision. They related mainly to controlled clinical trials, with external sponsors and investigators, carried out in low-resource countries and to the use of comparators other than an established effective intervention. The issue in question was the perceived need in those countries for low-cost, technologically appropriate, public-health solutions, and in particular for HIV/AIDS treatment drugs or vaccines that poorer countries could afford. Commentators took opposing sides on this issue. One advocated, for low-resource countries, trials of interventions that, while they might be less effective than the treatment available in the better-off countries, would be less expensive. All research efforts for public solutions appropriate to developing countries should not be rejected as unethical, they claimed. The research context should be considered. Local decision-making should be the norm. Paternalism on the part of the richer countries towards poorer countries should be avoided. The challenge was to encourage research for local solutions to the burden of disease in much of the world, while providing clear guidance on protecting against exploitation of vulnerable communities and individuals.

The other side argued that such trials constituted, or risked constituting, exploitation of poor countries by rich countries and were inherently unethical. Economic factors should not influence ethical considerations. It was within the capacity of rich countries or the pharmaceutical industry to make established effective treatment available for comparator purposes. Certain low-resource countries had already made available from their own resources established effective treatment for their HIV/AIDS patients.

This conflict complicated the revision and updating of the 1993 Guidelines. Ultimately, it became clear that the conflicting views could not be reconciled, though the proponents of the former view claimed that the new guidelines had built in effective safeguards against exploitation. The commentary to the Guideline concerned (11) recognizes the unresolved, or unresolvable, conflict.

The revision/updating of the 1993 Guidelines began in December 1998, and a first draft prepared by the CIOMS consultant for the project was reviewed by the project steering committee, which met in May 1999. The committee proposed amendments and listed topics on which new or revised guidelines were indicated; it recommended papers to be commissioned on the topics, as well as authors and commentators, for presentation and discussion at a CIOMS interim consultation. It was considered that an interim consultation meeting, of members of the steering committee together with the authors of commissioned papers and designated commentators, followed by further redrafting and electronic distribution and feedback, would better serve the purpose of the project than the process originally envisaged, which had been to complete the revision in one further step. The consultation was accordingly organized for March 2000, in Geneva.

At the consultation, progress on the revision was reported and contentious matters reviewed. Eight commissioned papers previously distributed were presented, commented upon, and discussed. The work of the consultation continued with ad hoc electronic working groups over the following several weeks, and the outcome was made available for the preparation of the third draft. The material commissioned for the consultation was made the subject of a CIOMS publication: *Biomedical Research Ethics: Updating International Guidelines. A Consultation* (December 2000).

An informal redrafting group of eight, from Africa, Asia, Latin America, the United States and the CIOMS secretariat met in New York City in January 2001, and subsequently interacted electronically with one another and with the CIOMS secretariat. A revised draft was posted on the CIOMS website in June 2001 and otherwise widely distributed. Many organizations and individuals commented, some

extensively, some critically. Views on certain positions, notably on placebo-controlled trials, were contradictory. For the subsequent revision two members were added to the redrafting group, from Europe and Latin America. The consequent draft was posted on the website in January 2002 in preparation for the CIOMS Conference in February/ March 2002

The CIOMS Conference was convened to discuss and, as far as possible, endorse a final draft to be submitted for final approval to the CIOMS Executive Committee. Besides representation of member organizations of CIOMS, participants included experts in ethics and research from all continents. They reviewed the draft guidelines seriatim and suggested modifications. Guideline 11, *Choice of control in clinical trials*, was redrafted at the conference in an effort to reduce disagreement. The redrafted text of that guideline was intensively discussed and generally well received. Some participants, however, continued to question the ethical acceptability of the exception to the general rule limiting the use of placebo to the conditions set out in the guideline; they argued that research subjects should not be exposed to risk of serious or irreversible harm when an established effective intervention could prevent such harm, and that such exposure could constitute exploitation. Ultimately, the commentary of Guideline 11 reflects the opposing positions on use of a comparator other than an established effective intervention for control purposes.

The new text, the 2002 text, which supersedes that of 1993, consists of a statement of general ethical principles, a preamble and 21 guidelines, with an introduction and a brief account of earlier declarations and guidelines. Like the 1982 and 1993 Guidelines, the present publication is designed to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects

Comments on the Guidelines are welcome and should be addressed to the Secretary-General, Council for International Organizations of Medical Sciences, c/o World Health Organization, CH-1211 Geneva 27, Switzerland; or by e-mail to cioms@who.int

INTRODUCTION

This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences since 1982. Its scope and preparation reflect well the transformation that has occurred in the field of research ethics in the almost quarter century since CIOMS first undertook to make this contribution to medical sciences and the ethics of research. The CIOMS Guidelines, with their stated concern for the application of the Declaration of Helsinki in developing countries, necessarily reflect the conditions and the needs of biomedical research in those countries, and the implications for multinational or transnational research in which they may be partners.

An issue, mainly for those countries and perhaps less pertinent now than in the past, has been the extent to which ethical principles are considered universal or as culturally relative – the universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care. The Guidelines take the position that research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards.

Related to this issue is that of the human rights of research subjects, as well as of health professionals as researchers in a variety of sociocultural contexts, and the contribution that international human rights instruments can make in the application of the general principles of ethics to research involving human subjects. The issue concerns largely, though not exclusively, two principles: respect for autonomy and protection of dependent or vulnerable persons and populations. In the preparation of the Guidelines the potential contribution in these respects of human rights instruments and norms was discussed, and the Guideline drafters have represented the views of commentators on safeguarding the corresponding rights of subjects.

Certain areas of research are not represented by specific guidelines. One such is human genetics. It is, however, considered in Guideline 18 Commentary under *Issues of confidentiality in genetics research.* The ethics of genetics research was the subject of a commissioned paper and commentary.

Another unrepresented area is research with products of conception (embryo and fetal research, and fetal tissue research). An attempt to craft a guideline on the topic proved unfeasible. At issue was the moral status of embryos and fetuses and the degree to which risks to the life or well-being of these entities are ethically permissible.

In relation to the use of comparators in controls, commentators have raised the the question of standard of care to be provided to a control group. They emphasize that standard of care refers to more than the comparator drug or other intervention, and that research subjects in the poorer countries do not usually enjoy the same standard of all-round care enjoyed by subjects in richer countries. This issue is not addressed specifically in the Guidelines.

In one respect the Guidelines depart from the terminology of the Declaration of Helsinki. ‘Best current intervention’ is the term most commonly used to describe the active comparator that is ethically preferred in controlled clinical trials. For many indications, however, there is more than one established ‘current’ intervention and expert clinicians do not agree on which is superior. In other circumstances in which there are several established ‘current’ interventions, some expert clinicians recognize one as superior to the rest; some commonly prescribe another because the superior intervention may be locally unavailable, for example, or prohibitively expensive or unsuited to the capability of particular patients to adhere to a complex and rigorous regimen. ‘Established effective intervention’ is the term used in Guideline 11 to refer to all such interventions, including the best and the various alternatives to the best. In some cases an ethical review committee may determine that it is ethically acceptable to use an established effective intervention as a comparator, even in cases where such an intervention is not considered the best current intervention.

The mere formulation of ethical guidelines for biomedical research involving human subjects will hardly resolve all the moral doubts that can arise in association with much research, but the Guidelines can at least draw the attention of sponsors, investigators and ethical review committees to the need to consider carefully the ethical implications of research protocols and the conduct of research, and thus conduce to high scientific and ethical standards of biomedical research.

INTERNATIONAL INSTRUMENTS AND GUIDELINES

The first international instrument on the ethics of medical research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians (the Doctors’ Trial) who had conducted atrocious experiments on unconsenting prisoners and detainees during the second world war. The Code, designed to protect the integrity of the research subject, set out conditions for the ethical conduct of

research involving human subjects, emphasizing their voluntary consent to research.

The Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations in 1948. To give the Declaration legal as well as moral force, the General Assembly adopted in 1966 the International Covenant on Civil and Political Rights. Article 7 of the Covenant states "*No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation"*. It is through this statement that society expresses the fundamental human value that is held to govern all research involving human subjects – the protection of the rights and welfare of all human subjects of scientific experimentation.

The Declaration of Helsinki, issued by the World Medical Association in 1964, is the fundamental document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration, amended several times, most recently in 2000 (Appendix 2), is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and nonclinical biomedical research.

Since the publication of the CIOMS 1993 Guidelines, several international organizations have issued ethical guidance on clinical trials. This has included, from the World Health Organization, in 1995, *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products*; and from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in 1996, *Guideline on Good Clinical Practice*, designed to ensure that data generated from clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan and the United States of America. The Joint United Nations Programme on HIV/AIDS published in 2000 the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research*.

In 2001 the Council of Ministers of the European Union adopted a Directive on clinical trials, which will be binding in law in the countries of the Union from 2004. The Council of Europe, with more than 40 member States, is developing a Protocol on Biomedical Research, which will be an additional protocol to the Council's 1997 Convention on Human Rights and Biomedicine.

Not specifically concerned with biomedical research involving human subjects but clearly pertinent, as noted above, are international human rights instruments. These are mainly the Universal Declaration of Human Rights, which, particularly in its science provisions, was highly influenced by the Nuremberg Code; the International Covenant on Civil and Political Rights; and the International Covenant on Economic, Social and Cultural Rights. Since the Nuremberg experience, human rights law has expanded to include the protection of women (Convention on the Elimination of All Forms of Discrimination Against Women) and children (Convention on the Rights of the Child). These and other such international instruments endorse in terms of human rights the general ethical principles that underlie the CIOMS International Ethical Guidelines.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The

present guidelines are directed at the application of these principles to research involving human subjects.

Respect for persons incorporates at least two fundamental ethical considerations, namely:

a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and

b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence refers to the ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, ***nonmaleficence*** (do no harm).

Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to ***distributive justice,*** which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons.

Sponsors of research or investigators cannot, in general, be held accountable for unjust conditions where the research is conducted, but they must refrain from practices that are likely to worsen unjust conditions or contribute to new inequities. Neither should they take advantage of the relative inability of low-resource countries or vulnerable populations to protect their own interests, by conducting research inexpensively and avoiding complex regulatory systems of industrialized countries in order to develop products for the lucrative markets of those countries.

In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.

Justice requires also that the research be responsive to the health conditions or needs of vulnerable subjects. The subjects selected should be the least vulnerable necessary to accomplish the purposes of the research. Risk to vulnerable subjects is most easily justified when it arises from interventions or procedures that hold out for them the prospect of direct health-related benefit. Risk that does not hold out such prospect must be justified by the anticipated benefit to the population of which the individual research subject is representative.

PREAMBLE

The term "research" refers to a class of activity designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In the present context "research" includes both medical and behavioural studies pertaining to human health. Usually "research" is modified by the adjective "biomedical" to indicate its relation to health.

Progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes or epidemiological findings, and requires at some time research involving human subjects. The collection, analysis and interpretation of information obtained from research involving human beings contribute significantly to the improvement of human health.

Research involving human subjects includes:

- studies of a physiological, biochemical or pathological process, or of the response to a specific intervention – whether physical, chemical or psychological – in healthy subjects or patients;

- controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;

- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and

- studies concerning human health-related behaviour in a variety of circumstances and environments.

Research involving human subjects may employ either observation or physical, chemical or psychological intervention; it may also either generate records or make use of existing records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in *International Guidelines for Ethical Review of Epidemiological Studies (CIOMS, 1991).*

The research may be concerned with the social environment, manipulating environmental factors in a way that could affect incidentally-exposed individuals. It is defined in broad terms in order to embrace field studies of pathogenic organisms and toxic chemicals under investigation for health-related purposes.

Biomedical research with human subjects is to be distinguished from the practice of medicine, public health and other forms of health care, which is designed to contribute directly to the health of individuals or communities. Prospective subjects may find it confusing when research and practice are to be conducted simultaneously, as when research is designed to obtain new information about the efficacy of a drug or other therapeutic, diagnostic or preventive modality.

As stated in Paragraph 32 of the Declaration of Helsinki, "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."

Professionals whose roles combine investigation and treatment have a special obligation to protect the rights and welfare of the patient-subjects. An investigator who agrees to act as physician-investigator undertakes some or 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, or to see that the subject receives the necessary care in the health-care system, or to offer assistance in finding another physician.

Research with human subjects should be carried out only by, or strictly supervised by, suitably qualified and experienced investigators and in accordance with a protocol that clearly states: the aim of the research; the reasons for proposing that it involve human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects' consent will be adequately informed and voluntary. The protocol should be scientifically and ethically appraised by one or more suitably constituted review bodies, independent of the investigators.

New vaccines and medicinal drugs, before being approved for general use, must be tested on human subjects in clinical trials; such trials constitute a substantial part of all research involving human subjects.

THE GUIDELINES

Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

Commentary on Guideline 1

Among the essential features of ethically justified research involving human subjects**,** including research with identifiable human tissue or data, are that the research offers a means of developing information not otherwise obtainable, that the design of the research is scientifically sound, and that the investigators and other research personnel are competent. The methods to be used should be appropriate to the objectives of the research and the field of study. Investigators and sponsors must also ensure that all who participate in the conduct of the research are qualified by virtue of their education and experience to perform competently in their roles. These considerations should be adequately reflected in the research

protocol submitted for review and clearance to scientific and ethical review committees (Appendix I).

Scientific review is discussed further in the Commentaries to Guidelines 2 and 3: *Ethical review committees* and *Ethical review of externally sponsored research. O*ther ethical aspects of research are discussed in the remaining guidelines and their commentaries. The protocol designed for submission for review and clearance to scientific and ethical review committees should include, when relevant, the items specified in Appendix I, and should be carefully followed in conducting the research.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

Commentary on Guideline 2

Ethical review committees may function at the institutional, local, regional, or national level, and in some cases at the international level. The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be offered or accepted for a review committee`s approval or clearance of a protocol.

Scientific review. According to the Declaration of Helsinki (*Paragraph 11*), medical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where indicated, animal experimentation. Scientific review must consider, inter alia, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety. Committees competent to review and approve scientific aspects of research proposals must be multidisciplinary**.**

Ethical review. The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. Scientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is ipso facto unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects` and researchers` time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound. Also, it considers provisions for monitoring of data and safety.

If the ethical review committee finds a research proposal scientifically sound, or verifies that a competent expert body has found it so, it should then consider whether any known or possible risks to the subjects are justified by the expected benefits, direct or indirect, and whether the proposed research methods will minimize harm and maximize benefit. (See Guideline 8: *Benefits and risks of study participation.)* If the proposal is sound and the balance of risks to anticipated benefits is reasonable, the committee should then determine whether the procedures proposed for obtaining informed consent are

satisfactory and those proposed for the selection of subjects are equitable.

Ethical review of emergency compassionate use of an investigational therapy. In some countries, drug regulatory authorities require that the so-called compassionate or humanitarian use of an investigational treatment be reviewed by an ethical review committee as though it were research. Exceptionally, a physician may undertake the compassionate use of an investigational therapy before obtaining the approval or clearance of an ethical review committee, provided three criteria are met**:** a patient needs emergency treatment, there is some evidence of possible effectiveness of the investigational treatment, and there is no other treatment available that is known to be equally effective or superior. Informed consent should be obtained according to the legal requirements and cultural standards of the community in which the intervention is carried out. Within one week the physician must report to the ethical review committee the details of the case and the action taken, and an independent health-care professional must confirm in writing to the ethical review committee the treating physician's judgment that the use of the investigational intervention was justified according to the three specified criteria. (See also Guideline 13 Commentary section: *Other vulnerable groups.)*

National (centralized) or local review. Ethical review committees may be created under the aegis of national or local health administrations, national (or centralized) medical research councils or other nationally representative bodies. In a highly centralized administration a national, or centralized, review committee may be constituted for both the scientific and the ethical review of research protocols. In countries where medical research is not centrally administered, ethical review is more effectively and conveniently undertaken at a local or regional level. The authority of a local ethical review committee may be confined to a single institution or may extend to all institutions in which biomedical research is carried out within a defined geographical area. The basic responsibilities of ethical review committees are:

- to determine that all proposed interventions, particularly the administration of drugs and vaccines or the use of medical devices or procedures under development, are acceptably safe to be undertaken in humans or to verify that another competent expert body has done so;
- to determine that the proposed research is scientifically sound or to verify that another competent expert body has done so;
- to ensure that all other ethical concerns arising from a protocol are satisfactorily resolved both in principle and in practice;
- to consider the qualifications of the investigators, including education in the principles of research practice, and the conditions of the research site with a view to ensuring the safe conduct of the trial; and
- to keep records of decisions and to take measures to follow up on the conduct of ongoing research projects.
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Committee membership. National or local ethical review committees should be so composed as to be able to provide complete and adequate review of the research proposals submitted to them. It is generally presumed that their membership 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 and to ensure that the rights of the research subjects will be respected. They should include both men and women. When uneducated or illiterate persons form the focus of a study they should also be considered for membership or invited to be represented and have their views

expressed.

A number of members should be replaced periodically with the aim of blending the advantages of experience with those of fresh perspectives.

A national or local ethical review committee responsible for reviewing and approving proposals for externally sponsored research should have among its members or consultants persons who are thoroughly familiar with the customs and traditions of the population or community concerned and sensitive to issues of human dignity.

Committees that often review research proposals directed at specific diseases or impairments, such as HIV/AIDS or paraplegia, should invite or hear the views of individuals or bodies representing patients with such diseases or impairments. Similarly, for research involving such subjects as children, students, elderly persons or employees, committees should invite or hear the views of their representatives or advocates.

To maintain the review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member`s objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, if to do so is clearly the appropriate action to take, either at the member`s own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members.

Multi-centre research. Some research projects are designed to be conducted in a number of centres 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 centre. Such studies include clinical trials, research designed for the evaluation of health service programmes, and various kinds of epidemiological research. For such studies, local ethical or scientific review committees are not normally authorized to change doses of drugs, to change inclusion or exclusion criteria, or to make other similar modifications. They should be fully empowered to prevent a study that they believe to be unethical. Moreover, changes that local review committees believe are necessary to protect the research subjects should be documented and reported to the research institution or sponsor responsible for the whole research programme for consideration and due action, to ensure that all other subjects can be protected and that the research will be valid across sites.

To ensure the validity of multi-centre research, any change in the protocol should be made at every collaborating centre or institution, or, failing this, explicit inter-centre comparability procedures must be introduced; changes made at some but not all will defeat the purpose of multi-centre research. For some multi-centre studies, scientific and ethical review may be facilitated by agreement among centres to accept the conclusions of a single review committee; its members could include a representative of the ethical review committee at each of the centres at which the research is to be conducted, as well as individuals competent to conduct scientific review. In other circumstances, a centralized review may be complemented by local review relating to the local participating investigators and institutions. The central committee could review the study from a scientific and ethical standpoint, and the local committees could verify the practicability of the study in their communities, including the

infrastructures, the state of training, and ethical considerations of local significance.

In a large multi-centre trial, individual investigators will not have authority to act independently, with regard to data analysis or to preparation and publication of manuscripts, for instance. Such a trial usually has a set of committees which operate under the direction of a steering committee and are responsible for such functions and decisions. The function of the ethical review committee in such cases is to review the relevant plans with the aim of avoiding abuses.

Sanctions. Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary. They should be required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies. Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards.

Sanctions imposed by governmental, institutional, 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 researchers and in sponsors the capacity for ethical conduct of research.

Should sanctions become necessary, they should be directed at the non-compliant researchers or sponsors. They may include fines or suspension of eligibility to receive research funding, to use investigational interventions, or to practise medicine. Unless there are persuasive reasons to do otherwise, editors should refuse to publish the results of research conducted unethically, and retract any articles that are subsequently found to contain falsified or fabricated data or to have been based on unethical research. Drug regulatory authorities should consider refusal to accept unethically obtained data submitted in support of an application for authorization to market a product. Such sanctions, however, may deprive of benefit not only the errant researcher or sponsor but also that segment of society intended to benefit from the research; such possible consequences merit careful consideration.

Potential conflicts of interest related to project support. Increasingly, biomedical studies receive funding from commercial firms. Such sponsors have good reasons to support research methods that are ethically and scientifically acceptable, but cases have arisen in which the conditions of funding could have introduced bias. It may happen that investigators have little or no input into trial design, limited access to the raw data, or limited participation in data interpretation, or that the results of a clinical trial may not be published if they are unfavourable to the sponsor's product. This risk of bias may also be associated with other sources of support, such as government or foundations. As the persons directly responsible for their work, investigators should not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, to prepare manuscripts, or to publish them. Investigators must also disclose potential or apparent conflicts of interest on their part to the ethical review committee or to other institutional committees designed to evaluate and manage such conflicts. Ethical review committees should therefore ensure that these conditions are met. See also *Multi-centre research*, above.

Guideline 3: Ethical review of externally sponsored research

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

Commentary on Guideline 3

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 organization or pharmaceutical company 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 sponsor 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. As far as possible, there must be assurance that the review is independent and that there is no conflict of interest that might affect the judgement of members of the review committees in relation to any aspect of the research. When the external sponsor is an international organization, its review of the research protocol must be in accordance with its own independent ethical-review procedures and standards.

Committees in the external sponsoring country or international organization have a special responsibility to determine whether the scientific methods are sound and suitable to the aims of the research; whether the drugs, vaccines, devices or procedures 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 sponsor or in another country; and whether the proposed research is in compliance with the ethical standards of the external sponsoring country or international organization.

Committees in the host country have a special responsibility to determine whether the objectives of the research are responsive to the health needs and priorities of that country. 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 in the host country, therefore, must have as either members or consultants persons with such understanding; it will then be in a favourable position to determine the acceptability of the proposed means of obtaining informed consent and otherwise respecting the rights of prospective subjects as well as of the means proposed to protect the welfare of the research subjects. Such persons should be able, for example, to indicate suitable members of the community to serve as intermediaries between investigators and subjects, and to advise on whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange and other customs and traditions.

When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol. In short, in respect of host countries either with developed capacity for independent ethical review or in which external sponsors and investigators are contributing substantially to such capacity, ethical review in the external, sponsoring country may be limited to ensuring compliance with broadly stated ethical standards. The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better

understanding of the cultural and moral values of the population in which it is proposed to conduct the research; it is also likely to be in a better position to monitor compliance in the course of a study. However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

Commentary on Guideline 4

General considerations. Informed consent is a decision to participate in research, taken 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. As an additional safeguard, it must always be complemented by independent ethical review of research proposals. This safeguard of independent review is particularly important as many individuals are limited in their capacity to give adequate informed consent; they include young children, adults with severe mental or behavioural disorders, and persons who are unfamiliar with medical concepts and technology (See Guidelines 13, 14, 15).

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 prospective subjects**,** by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures.

Language. Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that suits the individual's level of understanding. The investigator must bear in mind that the prospective subject`s ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system. It depends also on the investigator's ability and willingness to communicate with patience and sensitivity.

Comprehension. The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood.

Documentation of consent. Consent may be indicated in a number of ways. The subject may imply consent by 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 waiver of the requirement of a signed consent form if the research carries 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 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 subject's 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. Their wording should be cleared by the ethical review committee. When consent has been obtained orally, investigators are responsible for providing documentation or proof of consent.

Waiver of the consent requirement. 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. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (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.

Renewing consent. When material changes occur in the conditions or the procedures of a study, and also periodically in long-term studies, the investigator should once again seek informed consent from the subjects. For example, new information may have come to light, either from the study or from other sources, about the risks or benefits of products being tested or about alternatives to them. Subjects should be given such information promptly. In many clinical trials, results are not disclosed to subjects and investigators until the study is concluded. This is ethically acceptable if an ethical review committee has approved their non-disclosure.

Cultural considerations. In some cultures an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent. In some populations the use of a number of local languages may complicate the communication of information to potential subjects and the ability of an investigator to ensure that they truly understand it. Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. Sponsors and investigators should develop culturally appropriate ways to communicate information that is necessary for adherence to the standard required in the informed consent process. Also, they should describe and justify in the research protocol the procedure they plan to use in communicating information to subjects. For collaborative research in developing countries the research project should, if necessary, include the provision of resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

Consent to use for research purposes biological materials (including genetic material) from subjects in clinical trials. Consent forms for the research protocol should include a separate section for clinical-trial subjects who are requested to provide their consent for the use of their biological specimens for research. Separate consent may be appropriate in some cases (e.g., if investigators are requesting permission to conduct basic research which is not a necessary part of the clinical trial), but not in others

(e.g., the clinical trial requires the use of subjects' biological materials).

Use of medical records and biological specimens. Medical records and biological specimens taken in the course of clinical care may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed. Patients have a right to know that their records or specimens may be used for research. Refusal or reluctance of individuals to agree to participate would not be evidence of impracticability sufficient to warrant waiving informed consent. Records and specimens of individuals who have specifically rejected such uses in the past may be used only in the case of public health emergencies**.** (See Guideline 18 Commentary, *Confidentiality between physician and patient)*

Secondary use of research records or biological specimens. Investigators may want to use records or biological specimens that another investigator has used or collected for use, in another institution in the same or another country. This raises the issue of whether the records or specimens contain personal identifiers, or can be linked to such identifiers, and by whom. (See also Guideline 18: *Safeguarding confidentiality*) If informed consent or permission was required to authorize the original collection or use of such records or specimens for research purposes, secondary uses are generally constrained by the conditions specified in the original consent. Consequently, it is essential that the original consent process anticipate, to the extent that this is feasible, any foreseeable plans for future use of the records or specimens for research. Thus, in the original process of seeking informed consent a member of the research team should discuss with, and, when indicated, request the permission of, prospective subjects as to: i) whether there will or could be any secondary use and, if so, whether such secondary use will be limited with regard to the type of study that may be performed on such materials; ii) the conditions under which investigators will be required to contact the research subjects for additional authorization for secondary use; iii) the investigators' plans, if any, to destroy or to strip of personal identifiers the records or specimens; and iv) the rights of subjects to request destruction or anonymization of biological specimens or of records or parts of records that they might consider particularly sensitive, such as photographs, videotapes or audiotapes.

(See also Guidelines 5: *Obtaining informed consent: Essential information for prospective research subjects;* 6: *Obtaining informed consent: Obligations of sponsors and investigators;* and 7: *Inducement to participate.)*

Guideline 5: Obtaining informed consent: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. **that the individual is invited to participate in research, the reasons for considering the**

individual suitable for the research, and that participation is voluntary;

2. **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;**

3. **the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;**

4. **for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;**

5. **the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;**

6. **whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;**

7. **that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;**

8. **that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);**

9. **any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;**

10. **the direct benefits, if any, expected to result to subjects from participating in the research**

11. **the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;**

12. **whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;**

13. **any currently available alternative interventions or courses of treatment;**

14. **the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;**

15. **the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;**

16. **policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to**

immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;

17. **the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;**

18. **the possible research uses, direct or secondary, of the subject`s medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);**

19. **whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);**

20. **whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;**

21. **whether the investigator is serving only as an investigator or as both investigator and the subject`s physician;**

22. **the extent of the investigator's responsibility to provide medical services to the participant;**

23. **that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.**

24. **in what way, and by what organization, the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);**

25. **whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;**

26. **that an ethical review committee has approved or cleared the research protocol.**

Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators

Sponsors and investigators have a duty to:

- **refrain from unjustified deception, undue influence, or intimidation;**
- **seek consent only after ascertaining that the prospective subject has adequate understanding 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 – investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, *Documentation of consent*);

- **renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,**
- **renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.**

Commentary on Guideline 6

The investigator is responsible for ensuring the adequacy of informed consent from each subject. The person obtaining informed consent should be knowledgeable about the research and capable of answering questions from prospective subjects. Investigators in charge of the study must make themselves available to answer questions at the request of subjects. Any restrictions on the subject`s opportunity to ask questions and receive answers before or during the research undermines the validity of the informed consent.

In some types of research, potential subjects should receive counselling about risks of acquiring a disease unless they take precautions. This is especially true of HIV/AIDS vaccine research (UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research, Guidance Point 14).*

Withholding information and deception. Sometimes, to ensure the validity of research, investigators withhold certain information in the consent process. In biomedical research, this typically takes the form of withholding information about the purpose of specific procedures. For example, subjects in clinical trials are often not told the purpose of tests performed to monitor their compliance with the protocol, since if they knew their compliance was being monitored they might modify their behaviour and hence invalidate 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; after the conclusion of the study they are given the omitted information. In other cases, because a request for permission to withhold some information would jeopardize the validity of the research, subjects are not told that some information has been withheld until the research has been completed. Any such procedure must receive the explicit approval of the ethical review committee.

Active deception of subjects is considerably more controversial than simply withholding certain information. Lying to subjects is a tactic not commonly employed in biomedical research. Social and behavioural scientists, however, sometimes 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.

Some people maintain that active deception is never permissible. Others would permit it in certain circumstances. Deception is not permissible, however, in cases in which the deception itself would disguise the possibility of the subject being exposed to more than minimal risk. When deception is deemed indispensable to the methods of a study the investigators 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 should determine the consequences for the subject of being deceived, and 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 should be offered an opportunity to refuse to allow the investigator to use information thus obtained. Investigators and ethical review committees should be aware that deceiving research subjects may wrong them as well as harm them; subjects may resent not having been informed when they learn that they have participated in a study under false pretences. In some studies there may be justification for deceiving persons other than the subjects by either withholding or disguising elements of information. Such tactics are often proposed, for example, for studies of the abuse of spouses or children. An ethical review committee must review and approve all proposals to deceive persons other than the subjects. Subjects are entitled to prompt and honest answers to their questions; the ethical review committee must determine for each study whether others who are to be deceived are similarly entitled.

Intimidation and undue influence. Intimidation in any form invalidates informed consent. Prospective subjects who are patients often depend for medical care upon the physician/investigator, who consequently has a certain credibility in their eyes, and whose influence over them may be considerable, particularly if the study protocol has a therapeutic component**.** They may fear, for example, that refusal to participate would damage the therapeutic relationship or result in the withholding of health services. The physician/investigator must assure them that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation the ethical review committee should consider whether a neutral third party should seek informed consent.

The prospective subject must not be exposed to undue influence. The borderline between justifiable persuasion and undue influence is imprecise, however. The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject's decision. (See also Guideline 4: *Individual informed consent.)*

Risks. Investigators should be completely objective in discussing the details of the experimental intervention, the pain and discomfort that it may entail, and known risks and possible hazards. In complex research projects it may be neither feasible nor desirable to inform prospective participants fully about every possible risk. They must, however, be informed of all risks that a ‘reasonable person’ would consider material to making a decision about whether to participate, including risks to a spouse or partner associated with trials of, for example, psychotropic or genital-tract medicaments. (See also Guideline 8 Commentary, *Risks to groups of persons.*)

Exception to the requirement for informed consent in studies of emergency situations in which the researcher anticipates that many subjects will be unable to consent. Research protocols are sometimes designed to address conditions occurring suddenly and rendering the patients/subjects incapable of giving informed consent. Examples are head trauma, cardiopulmonary arrest and stroke. The investigation cannot be done with patients who can give informed consent in time and there may not be time to locate a person having the authority to give permission. In such circumstances it is often necessary to proceed with the research interventions very soon after the onset of the condition in order to evaluate an investigational treatment or develop the desired knowledge. As this class of emergency exception can be anticipated, the researcher must secure the review and approval of an ethical review committee before initiating the study. If possible, an attempt should be made to identify a population that is likely to develop the condition to be studied. This can be done readily, for example, if the condition is one that recurs periodically in individuals; examples include grand mal seizures and alcohol binges. In such cases, prospective subjects should be contacted while fully capable of informed consent, and invited to consent to their involvement as research subjects during future periods of incapacitation. If they are patients of an independent physician who is also the physician-researcher, the physician should likewise seek their consent while they are fully capable of informed consent. In all cases in which

approved research has begun without prior consent of patients/subjects incapable of giving informed consent because of suddenly occurring conditions, they should be given all relevant information as soon as they are in a state to receive it, and their consent to continued participation should be obtained as soon as is reasonably possible**.**

Before proceeding without prior informed consent, the investigator must make reasonable efforts to locate an individual who has the authority to give permission on behalf of an incapacitated patient. If such a person can be located and refuses to give permission, the patient may not be enrolled as a subject**.** The risks of all interventions and procedures will be justified as required by Guideline 9 (*Special limitations on risks when research involves individuals who are not capable of giving consent).* The researcher and the ethical review committee should agree to a maximum time of involvement of an individual without obtaining either the individual's informed consent or authorization according to the applicable legal system if the person is not able to give consent. If by that time the researcher has not obtained either consent or permission – owing either to a failure to contact a representative or to a refusal of either the patient or the person or body authorized to give permission – the participation of the patient as a subject must be discontinued. The patient or the person or body providing authorization should be offered an opportunity to forbid the use of data derived from participation of the patient as a subject without consent or permission.

Where appropriate, plans to conduct emergency research without prior consent of the subjects should be publicized within the community in which it will be carried out. In the design and conduct of the research, the ethical review committee, the investigators and the sponsors should be responsive to the concerns of the community. If there is cause for concern about the acceptability of the research in the community, there should be a formal consultation with representatives designated by the community. The research should not be carried out if it does not have substantial support in the community concerned. (See Guideline 8 Commentary, *Risks to groups of persons*.)

Exception to the requirement of informed consent for inclusion in clinical trials of persons rendered incapable of informed consent by an acute condition. Certain patients with an acute condition that renders them incapable of giving informed consent may be eligible for inclusion in a clinical trial in which the majority of prospective subjects will be capable of informed consent. Such a trial would relate to a new treatment for an acute condition such as sepsis, stroke or myocardial infarction. The investigational treatment would hold out the prospect of direct benefit and would be justified accordingly, though the investigation might involve certain procedures or interventions that were not of direct benefit but carried no more than minimal risk; an example would be the process of randomization or the collection of additional blood for research purposes. For such cases the initial protocol submitted for approval to the ethical review committee should anticipate that some patients may be incapable of consent, and should propose for such patients a form of proxy consent, such as permission of the responsible relative. When the ethical review committee has approved or cleared such a protocol, an investigator may seek the permission of the responsible relative and enrol such a patient.

Guideline 7: Inducement to participate

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for

inconvenience and time spent. The payments should not be so large, however, 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 provided to research subjects must have been approved by an ethical review committee.

Commentary on Guideline 7

Acceptable recompense. Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research may also receive a small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

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 or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; local ethical review committees may find such inducements acceptable. Monetary and in-kind recompense must, therefore, 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. When research interventions or procedures that do not hold out the prospect of direct benefit present more than minimal risk, all parties involved in the research – sponsors, investigators and ethical review committees – in both funding and host countries should be careful to avoid undue material inducement.

Incompetent persons. Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

Withdrawal from a study. A subject who withdraws from research for reasons related to the study, such as unacceptable side-effects of a study drug, or who is withdrawn on health grounds, should be paid or recompensed as if full participation had taken place. A subject who withdraws for any other reason should be paid 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 8: Benefits and risks of study participation

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

- **Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they**

will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial' interventions or procedures must be justified in relation to expected benefits to the individual subject.

- **Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.**

Commentary on Guideline 8

The Declaration of Helsinki in several paragraphs deals with the well-being of research subjects and the avoidance of risk. Thus, considerations related to the well-being of the human subject should take precedence over the interests of science and society *(Paragraph 5*); clinical testing must be preceded by adequate laboratory or animal experimentation to demonstrate a reasonable probability of success without undue risk (*Paragraph 11*); every project should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others (*Paragraph 16*); physician-researchers must be confident that the risks involved have been adequately assessed and can be satisfactorily managed (*Paragraph 17*); and the risks and burdens to the subject must be minimized, and reasonable in relation to the importance of the objective or the knowledge to be gained (*Paragraph 18*).

Biomedical research often employs a variety of interventions of which some hold out the prospect of direct therapeutic benefit (beneficial interventions) and others are administered solely to answer the research question (non-beneficial interventions). Beneficial interventions are justified as they are in medical practice by the expectation that they will be at least as advantageous to the individuals concerned, in the light of both risks and benefits, as any available alternative. Non-beneficial interventions are assessed differently; they may be justified only by appeal to the knowledge to be gained. In assessing the risks and benefits that a protocol presents to a population, it is appropriate to consider the harm that could result from forgoing the research.

Paragraphs 5 and 18 of the Declaration of Helsinki do not preclude well-informed volunteers, capable of fully appreciating risks and benefits of an investigation, from participating in research for altruistic reasons or for modest remuneration.

Minimizing risk associated with participation in a randomized controlled trial. In randomized controlled trials subjects risk being allocated to receive the treatment that proves inferior. They are allocated by chance to one of two or more intervention arms and followed to a predetermined end-point. (Interventions are understood to include new or established therapies, diagnostic tests and preventive measures.) An intervention is evaluated by comparing it with another intervention (a control), which is ordinarily the best current method, selected from the safe and effective treatments available globally, unless some other control intervention such as placebo can be justified ethically (See Guideline 11).

To minimize risk when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator must not, for purposes of conducting the trial, withhold therapy that is known to be superior to the intervention being tested, unless the withholding can be justified by the standards set forth in Guideline 11. Also, the investigator must provide in the research protocol for the monitoring of research data by an independent board (Data and Safety Monitoring Board); one function of such a board is to protect the research subjects from previously unknown adverse reactions or unnecessarily prolonged exposure to an inferior therapy.

Normally at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

Risks to groups of persons. Research in certain fields, such as epidemiology, genetics or sociology, may present risks to the interests of communities, societies, or racially or ethnically defined groups. Information might be published that could stigmatize a group or expose its members to discrimination. Such information, for example, could indicate, rightly or wrongly, that the group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or is particularly susceptible to certain genetic disorders. Plans to conduct such research should be sensitive to such considerations, to the need to maintain confidentiality during and after the study, and to the need to publish the resulting data in a manner that is respectful of the interests of all concerned, or in certain circumstances not to publish them. The ethical review committee should ensure that the interests of all concerned are given due consideration; often it will be advisable to have individual consent supplemented by community consultation.

[The ethical basis for the justification of risk is elaborated further in Guideline 9]

Guideline 9*: *Special limitations on risk when research involves individuals who are not capable of giving informed consent

When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.

Commentary on Guideline 9

The low-risk standard: Certain individuals or groups may have limited capacity to give informed consent either because, as in the case of prisoners, their autonomy is limited, or because they have limited cognitive capacity. For research involving persons who are unable to consent, or whose capacity to make an informed choice may not fully meet the standard of informed consent, ethical review committees must distinguish between intervention risks that do not exceed those associated with routine medical or psychological examination of such persons and risks in excess of those.

When the risks of such interventions do not exceed those associated with routine medical or psychological examination of such persons, there is no requirement for special substantive or procedural protective measures apart from those generally required for all research involving members of the particular class of persons. When the risks are in excess of those, the ethical review committee must find: 1) that the research is designed to be responsive to the disease affecting the prospective subjects or to conditions to which they are particularly susceptible; 2) that the risks of the research interventions are only slightly greater than those associated with routine medical or psychological examination of such persons for the condition or set of clinical circumstances under investigation; 3) that the objective of the research is sufficiently important to justify exposure of the subjects to the increased risk; and 4) that the interventions are reasonably commensurate with the clinical interventions that the subjects have

experienced or may be expected to experience in relation to the condition under investigation.

If such research subjects, including children, become capable of giving independent informed consent during the research, their consent to continued participation should be obtained.

There is no internationally agreed, precise definition of a "slight or minor increase" above the risks associated with routine medical or psychological examination of such persons. Its meaning is inferred from what various ethical review committees have reported as having met the standard. Examples include additional lumbar punctures or bone-marrow aspirations in children with conditions for which such examinations are regularly indicated in clinical practice. The requirement that the objective of the research be relevant to the disease or condition affecting the prospective subjects rules out the use of such interventions in healthy children.

The requirement that the research interventions be reasonably commensurate with clinical interventions that subjects may have experienced or are likely to experience for the condition under investigation is intended to enable them to draw on personal experience as they decide whether to accept or reject additional procedures for research purposes. Their choices will, therefore, be more informed even though they may not fully meet the standard of informed consent.

(See also Guidelines 4: *Individual informed consent*; 13: *Research involving vulnerable persons;* 14: *Research involving children;* and 15: *Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent.)*

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- **the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and**
- **any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.**

Commentary on Guideline 10

This guideline is concerned with countries or communities in which resources are limited to the extent that they are, or may be, vulnerable to exploitation by sponsors and investigators from the relatively wealthy countries and communities.

Responsiveness of research to health needs and priorities. The ethical requirement that research be responsive to the health needs of the population or community in which it is carried out calls for decisions on what is needed to fulfil the requirement**.** It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of "responsiveness" can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population. This is applicable especially to research conducted in countries where

governments lack the resources to make such products or benefits widely available. Even when a product to be tested in a particular country is much cheaper than the standard treatment in some other countries, the government or individuals in that country may still be unable to afford it. If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical**.**

When an investigational intervention has important potential for health care in the host country, the negotiation that the sponsor should undertake to determine the practical implications of "responsiveness", as well as "reasonable availability", should include representatives of stakeholders in the host country; these include the national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups. The negotiation should cover the health-care infrastructure required for safe and rational use of the intervention, the likelihood of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when this economic information is not proprietary. In some cases, satisfactory discussion of the availability and distribution of successful products will necessarily engage international organizations, donor governments and bilateral agencies, international nongovernmental organizations, and the private sector. The development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of the research.

Additionally, if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority. The sponsor is unlikely to be in a position to make a beneficial investigational intervention generally available to the community or population until some time after the conclusion of the study, as it may be in short supply and in any case cannot be made generally available before a drug regulatory authority has approved it.

For minor research studies and when the outcome is scientific knowledge rather than a commercial product, such complex planning or negotiation is rarely, if ever, needed. There must be assurance, however, that the scientific knowledge developed will be used for the benefit of the population.

Reasonable availability. The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the community or population concerned; the severity of a subject’s medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.

In general, if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research, it is unethical to conduct the research in that country or community. This should not be construed as precluding studies designed to evaluate novel therapeutic concepts. As a rare exception, for example, research may be designed to obtain preliminary evidence that a drug or a class of drugs has a beneficial effect in the treatment of a disease that occurs only in regions with extremely limited resources, and it could not be carried out reasonably well in more developed communities. Such research may be justified ethically even if there is no plan in place to make a product available to the population of the host country or community at the conclusion of the preliminary phase of its development. If the concept is found to be valid, subsequent phases of the research could result in a product that could be made reasonably available at its

conclusion.

(See also Guidelines 3: *Ethical review of externally sponsored research;* 12, *Equitable distribution of burdens and benefits;* 20: *Strengthening capacity for ethical and scientific review and biomedical research;* and 21: *Ethical obligation of external sponsors to provide health-care services.)*

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".

Placebo may be used:

- **when there is no established effective intervention;**
- **when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;**
- **when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.**

Commentary on Guideline 11

General considerations for controlled clinical trials. The design of trials of investigational diagnostic, therapeutic or preventive interventions raises interrelated scientific and ethical issues for sponsors, investigators and ethical review committees**.** To obtain reliable results, investigators must compare the effects of an investigational intervention on subjects assigned to the investigational arm (or arms) of a trial with the effects that a control intervention produces in subjects drawn from the same population and assigned to its control arm. Randomization is the preferred method for assigning subjects to the various arms of the clinical trial unless another method**,** such as historical or literature controls, can be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial.

A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results. When the objective is to establish the effectiveness and safety of an investigational intervention, the use of a placebo control is often much more likely than that of an active control to produce a scientifically reliable result. In many cases the ability of a trial to distinguish effective from ineffective interventions (its assay sensitivity) cannot be assured unless the control is a placebo. If, however, an effect of using a placebo would be to deprive subjects in the control arm of an established effective intervention, and thereby to expose them to serious harm, particularly if it is irreversible, it would obviously be unethical to use a placebo.

Placebo control in the absence of a current effective alternative. The use of placebo in the control arm of a clinical trial is ethically acceptable when, as stated in the Declaration of Helsinki (Paragraph 29), "no proven prophylactic, diagnostic or therapeutic method exists." Usually, in this case, a placebo is scientifically preferable to no intervention. In certain circumstances, however, an alternative design may be both scientifically and ethically acceptable, and preferable; an example would be a clinical trial of a surgical intervention, because, for many surgical interventions, either it is not possible or it is ethically unacceptable to devise a suitable placebo; for another example, in certain vaccine trials an investigator might choose to provide for those in the 'control' arm a vaccine that is unrelated to the investigational vaccine.

Placebo-controlled trials that entail only minor risks. A placebo-controlled design may be ethically acceptable, and preferable on scientific grounds, when the condition for which patients/subjects are randomly assigned to placebo or active treatment is only a small deviation in physiological measurements, such as slightly raised blood pressure or a modest increase in serum cholesterol; and if delaying or omitting available treatment may cause only temporary discomfort (e.g., common headache) and no serious adverse consequences. The ethical review committee must be fully satisfied that the risks of withholding an established effective intervention are truly minor and short-lived.

Placebo control when active control would not yield reliable results. A related but distinct rationale for using a placebo control rather than an established effective intervention is that the documented experience with the established effective intervention is not sufficient to provide a scientifically reliable comparison with the intervention being investigated; it is then difficult, or even impossible, without using a placebo, to design a scientifically reliable study. This is not always, however, an ethically acceptable basis for depriving control subjects of an established effective intervention in clinical trials; only when doing so would not add any risk of serious harm, particularly irreversible harm, to the subjects would it be ethically acceptable to do so. In some cases, the condition at which the intervention is aimed (for example, cancer or HIV/AIDS) will be too serious to deprive control subjects of an established effective intervention.

This latter rationale (*when active control would not yield reliable results)* differs from the former *(trials that entail only minor risks)* in emphasis. In trials that entail only minor risks the investigative interventions are aimed at relatively trivial conditions, such as the common cold or hair loss; forgoing an established effective intervention for the duration of a trial deprives control subjects of only minor benefits. It is for this reason that it is not unethical to use a placebo-control design. Even if it were possible to design a so-called "non-inferiority", or "equivalency", trial using an active control, it would still not be unethical in these circumstances to use a placebo-control design. In any event, the researcher must satisfy the ethical review committee that the safety and human rights of the subjects will be fully protected, that prospective subjects will be fully informed about alternative treatments, and that the purpose and design of the study are scientifically sound. The ethical acceptability of such placebo-controlled studies increases as the period of placebo use is decreased, and when the study design permits change to active treatment ("escape treatment") if intolerable symptoms occur.

Exceptional use of a comparator other than an established effective intervention. An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable. Accordingly, the proposed investigational intervention must be responsive to the health needs of the population from which the research subjects are recruited and there must be assurance that, if it proves to be safe and

effective, it will be made reasonably available to that population. Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy.

However, some people strongly object to the exceptional use of a comparator other than an established effective intervention because it could result in exploitation of poor and disadvantaged populations. The objection rests on three arguments:

- Placebo control could expose research subjects to risk of serious or irreversible harm when the use of an established effective intervention as comparator could avoid the risk.
- Not all scientific experts agree about conditions under which an established effective intervention used as a comparator would not yield scientifically reliable results.
- An economic reason for the unavailability of an established effective intervention cannot justify a placebo-controlled study in a country of limited resources when it would be unethical to conduct a study with the same design in a population with general access to the effective intervention outside the study.

Placebo control when an established effective intervention is not available in the host country. The question addressed here is: when should an exception be allowed to the general rule that subjects in the control arm of a clinical trial should receive an established effective intervention?

The usual reason for proposing the exception is that, for economic or logistic reasons, an established effective intervention is not in general use or available in the country in which the study will be conducted, whereas the investigational intervention could be made available, given the finances and infrastructure of the country.

Another reason that may be advanced for proposing a placebo-controlled trial is that using an established effective intervention as the control would not produce scientifically reliable data relevant to the country in which the trial is to be conducted. Existing data about the effectiveness and safety of the established effective intervention may have been accumulated under circumstances unlike those of the population in which it is proposed to conduct the trial**;** this, it may be argued, could make their use in the trial unreliable. One reason could be that the disease or condition manifests itself differently in different populations, or other uncontrolled factors could invalidate the use of existing data for comparative purposes.

The use of placebo control in these circumstances is ethically controversial, for the following reasons:

- Sponsors of research might use poor countries or communities as testing grounds for research that would be difficult or impossible in countries where there is general access to an established effective intervention, and the investigational intervention, if proven safe and effective, is likely to be marketed in countries in which an established effective intervention is already available and it is not likely to be marketed in the host country.
- The research subjects, both active-arm and control-arm, are patients who may have a serious, possibly life-threatening, illness. They do not normally have access to an established effective

intervention currently available to similar patients in many other countries. According to the requirements of a scientifically reliable trial, investigators, who may be their attending physicians, would be expected to enrol some of those patients/subjects in the placebo-control arm. This would appear to be a violation of the physician's fiduciary duty of undivided loyalty to the patient, particularly in cases in which known effective therapy could be made available to the patients.

An argument for exceptional use of placebo control may be that a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, seeks to develop an affordable intervention specifically for a health problem affecting its population. There may then be less reason for concern that a placebo design is exploitative, and therefore unethical, as the health authority has responsibility for the population`s health, and there are valid health grounds for testing an apparently beneficial intervention. In such circumstances an ethical review committee may determine that the proposed trial is ethically acceptable, provided that the rights and safety of subjects are safeguarded**.**

Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established effective intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country. This may be difficult to determine, however, as it is clear that, with sufficient persistence and ingenuity, ways may be found of accessing previously unattainable medicinal products, and thus avoiding the ethical issue raised by the use of placebo control.

When the rationale of proposing a placebo-controlled trial is that the use of an established effective intervention as the control would not yield scientifically reliable data relevant to the proposed host country, the ethical review committee in that country has the option of seeking expert opinion as to whether use of an established effective intervention in the control arm would invalidate the results of the research.

An "equivalency trial" as an alternative to a placebo-controlled trial. An alternative to a placebo-control design in these circumstances would be an "equivalency trial", which would compare an investigational intervention with an established effective intervention and produce scientifically reliable data. An equivalency trial in a country in which no established effective intervention is available is not designed to determine whether the investigational intervention is superior to an established effective intervention currently used somewhere in the world; its purpose is, rather, to determine whether the investigational intervention is, in effectiveness and safety, equivalent to, or almost equivalent to, the established effective intervention. It would be hazardous to conclude, however, that an intervention demonstrated to be equivalent, or almost equivalent, to an established effective intervention is better than nothing or superior to whatever intervention is available in the country; there may be substantial differences between the results of superficially identical clinical trials carried out in different countries. If there are such differences, it would be scientifically acceptable and ethically preferable to conduct such 'equivalency' trials in countries in which an established effective intervention is already available.

If there are substantial grounds for the ethical review committee to conclude that an established effective intervention will not become available and implementable, the committee should obtain assurances from the parties concerned that plans have been agreed for making the investigational intervention reasonably available in the host country or community once its effectiveness and safety have been established. Moreover, when the study has external sponsorship, approval should usually be dependent on the sponsors and the health authorities of the host country having engaged in a process of negotiation and

planning, including justifying the study in regard to local health-care needs.

Means of minimizing harm to placebo-control subjects. Even when placebo controls are justified on one of the bases set forth in the guideline, there are means of minimizing the possibly harmful effect of being in the control arm.

First, a placebo-control group need not be untreated. An add-on design may be employed when the investigational therapy and a standard treatment have different mechanisms of action. The treatment to be tested and placebo are each added to a standard treatment. Such studies have a particular place when a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret [*International Conference on Harmonisation* (*ICH) Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000*]. In testing for improved treatment of life-threatening diseases such as cancer, HIV/AIDS, or heart failure, add-on designs are a particularly useful means of finding improvements in interventions that are not fully effective or may cause intolerable side-effects. They have a place also in respect of treatment for epilepsy, rheumatism and osteoporosis, for example, because withholding of established effective therapy could result in progressive disability, unacceptable discomfort or both.

Second, as indicated in Guideline 8 Commentary, when the intervention to be tested in a randomized controlled trial is designed to prevent or postpone a lethal or disabling outcome, the investigator minimizes harmful effects of placebo-control studies by providing in the research protocol for the monitoring of research data by an independent Data and Safety Monitoring Board (DSMB). One function of such a board is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior therapy. The board fulfils the latter function by means of interim analyses of the data pertaining to efficacy to ensure that the trial does not continue beyond the point at which an investigational therapy is demonstrated to be effective. Normally, at the outset of a randomized controlled trial, criteria are established for its premature termination (stopping rules or guidelines).

In some cases the DSMB is called upon to perform "conditional power calculations", designed to determine the probability that a particular clinical trial could ever show that the investigational therapy is effective. If that probability is very small, the DSMB is expected to recommend termination of the clinical trial, because it would be unethical to continue it beyond that point.

In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study.

Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research

Groups 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. The exclusion of

groups or communities that might benefit from study participation must be justified.

Commentary on Guideline 12

General considerations: Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term; such benefits include the direct benefits of participation as well as the benefits of the new knowledge that the research is designed to yield. When burdens or benefits of research are to be apportioned unequally among individuals or groups of persons, the criteria for unequal distribution should be morally justifiable and not arbitrary. In other words, unequal allocation must not be inequitable. Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status or gender unless there is a sound scientific reason to do otherwise.

In the past, groups of persons were excluded from participation in research for what were then considered good reasons. As a consequence of such exclusions, information about the diagnosis, prevention and treatment of diseases in such groups of persons is limited. This has resulted in a serious class injustice. If information about the management of diseases is considered a benefit that is distributed within a society, it is unjust to deprive groups of persons of that benefit. Such documents as the Declaration of Helsinki and the UNAIDS Guidance Document *Ethical Considerations in HIV Preventive Vaccine Research,* and the policies of many national governments and professional societies, recognize the need to redress these injustices by encouraging the participation of previously excluded groups in basic and applied biomedical research.

Members of vulnerable groups also have the same entitlement to access to the benefits of investigational interventions that show promise of therapeutic benefit as persons not considered vulnerable, particularly when no superior or equivalent approaches to therapy are available.

There has been a perception, sometimes correct and sometimes incorrect, that certain groups of persons have been overused as research subjects. In some cases such overuse has been based on the administrative availability of the populations. Research hospitals are often located in places where members of the lowest socioeconomic classes reside, and this has resulted in an apparent overuse of such persons. Other groups that may have been overused because they were conveniently available to researchers include students in investigators' classes, residents of long-term care facilities and subordinate members of hierarchical institutions. Impoverished groups have been overused because of their willingness to serve as subjects in exchange for relatively small stipends. Prisoners have been considered ideal subjects for Phase I drug studies because of their highly regimented lives and, in many cases, their conditions of economic deprivation.

Overuse of certain groups, such as the poor or the administratively available, is unjust for several reasons. It is unjust to selectively recruit impoverished people to serve as research subjects simply because they can be more easily induced to participate in exchange for small payments. In most cases, these people would be called upon to bear the burdens of research so that others who are better off could enjoy the benefits. However, although the burdens of research should not fall disproportionately on socio-economically disadvantaged groups, neither should such groups be categorically excluded from research protocols. It would not be unjust to selectively recruit poor people to serve as subjects in research designed to address problems that are prevalent in their group – malnutrition, for example. Similar considerations apply to institutionalized groups or those whose availability to the investigators is for other reasons administratively convenient.

Not only may certain groups within a society be inappropriately overused as research subjects, but also entire communities or societies may be overused. This has been particularly likely to occur in countries or communities with insufficiently well-developed systems for the protection of the rights and welfare of human research subjects. Such overuse is especially questionable when the populations or communities concerned bear the burdens of participation in research but are extremely unlikely ever to enjoy the benefits of new knowledge and products developed as a result of the research. (See Guideline 10: *Research in populations and communities with limited resources.)*

Guideline 13: Research involving vulnerable persons

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Commentary on Guideline 13

Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

General considerations. The central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of the burdens and benefits of research participation. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (Guidelines 14,15) and include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that:

- the research could not be carried out equally 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 interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and,
- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

Other vulnerable 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, whether justified or not, by the expectation of preferential treatment if they agree 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, 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.

Elderly persons are commonly regarded as vulnerable. With advancing age**,** people are increasingly likely to acquire attributes that define them as vulnerable. They may, for example, be institutionalized or develop varying degrees of dementia**.** If and when they acquire such vulnerability-defining attributes, and not before, it is appropriate to consider them vulnerable and to treat them accordingly.

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 or displaced persons, prisoners, patients with incurable disease, individuals who are politically powerless, and members of communities unfamiliar with modern medical concepts. 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 reviewed and applied, where relevant.

Persons who have serious, potentially disabling or life-threatening diseases are highly vulnerable**.** Physicians sometimes treat such patients with drugs or other therapies not yet licensed for general availability because studies designed to establish their safety and efficacy have not been completed. This is compatible with the Declaration of Helsinki, which states in Paragraph 32*: " In the treatment of a patient, where proven…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… therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering"*. Such treatment, commonly called 'compassionate use', is not properly regarded as research, but it can contribute to ongoing research into the safety and efficacy of the interventions used.

Although, on the whole, investigators must study less vulnerable groups before involving more vulnerable groups, some exceptions are justified. In general, children are not suitable for Phase I drug trials or for Phase I or II vaccine trials, but such trials may be permissible after studies in adults have shown some therapeutic or preventive effect. For example, a Phase II vaccine trial seeking evidence of immunogenicity in infants may be justified when a vaccine has shown evidence of preventing or slowing progression of an infectious disease in adults, or Phase I research with children may be appropriate because the disease to be treated does not occur in adults or is manifested differently in children (Appendix 3: *The phases of clinical trials of vaccines and drugs*).

Guideline 14: Research involving children

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

- **the research might not 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 representative of each child has given permission;**
- **the agreement (assent) of each child has been obtained to the extent of the child`s capabilities; and,**
- **a child`s refusal to participate or continue in the research will be respected.**

Commentary on Guideline 14

Justification of the involvement of children in biomedical research. The participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible (cf. vaccine trials*)*, as well as for clinical trials of drugs that are designed for children as well as adults. In the past, many new products were not tested for children though they were directed towards diseases also occurring in childhood; thus children either did not benefit from these new drugs or were exposed to them though little was known about their specific effects or safety in children**.** Now it is widely agreed that, as a general rule, the sponsor of any new therapeutic, diagnostic or preventive product that is likely to be indicated for use in children is obliged to evaluate its safety and efficacy for children before it is released for general distribution.

Assent 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**,** sometimes referred to as assent**,** is insufficient to permit participation in research unless it is supplemented by the permission of a parent, a legal guardian or other duly authorized representative.

Some children who are too immature to be able to give knowing agreement, or assent, may be able to register a 'deliberate objection', an expression of disapproval or refusal of a proposed procedure. The deliberate objection of an older child, for example, is to be distinguished from the behaviour of an infant, who is likely to cry or withdraw in response to almost any stimulus. Older children, who are more capable of giving assent, should be selected before younger children or infants, unless there are valid scientific reasons related to age for involving younger children first.

A deliberate objection by a child to taking part in research should always be respected even if the parents have given permission, unless the child needs treatment that is not available outside the context of research, the investigational intervention shows promise of therapeutic benefit, and there is no acceptable alternative therapy. In such a case, particularly if the child is very young or immature, a parent or guardian may override the child`s objections. If the child is older and more nearly capable of independent informed consent, the investigator should seek the specific approval or clearance of the scientific and ethical review committees for initiating or continuing with the investigational treatment. If child subjects become capable of independent informed consent during the research, their informed consent to continued participation should be sought and their decision respected.

A child with a likely fatal illness may object or refuse assent to continuation of a burdensome or distressing intervention. In such circumstances parents may press an investigator to persist with an investigational intervention against the child`s wishes. The investigator may agree to do so if the intervention shows promise of preserving or prolonging life and there is no acceptable alternative treatment. In such cases, the investigator should seek the specific approval or clearance of the ethical review committee before agreeing to override the wishes of the child.

Permission of a parent or guardian. The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures. It may be assumed that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission. Even when the law requires parental permission, however, the assent of the child must be obtained.

In some jurisdictions, some individuals who are below the general age of consent are regarded as "emancipated" or "mature" minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. They may be married or pregnant or be already parents or living independently. Some studies involve investigation of adolescents' beliefs and behaviour regarding sexuality or use of recreational drugs; other research addresses domestic violence or child abuse. For studies on these topics, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the adolescents at some risk of questioning or even intimidation by their parents.

Because of the issues inherent in obtaining assent from children in institutions, such children should only exceptionally be subjects of research. In the case of institutionalized children without parents, or whose parents are not legally authorized to grant permission, the ethical review committee may require sponsors or investigators to provide it with the opinion of an independent, concerned, expert advocate for institutionalized children as to the propriety of undertaking the research with such children.

Observation of research by a parent or guardian. A parent or guardian who gives permission for a child to participate in research should be given the opportunity, to a reasonable extent, to observe the research as it proceeds, so as to be able to withdraw the child 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, paediatrician or other health-care provider on matters concerning the child's participation in the research.

(See also Guideline 8: *Benefits and risks of study participation*; Guideline 9: *Special limitations on risks when subjects are not capable of giving consent*; and Guideline 13: *Research involving vulnerable persons.)*

Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are

not capable of giving adequately informed consent

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 whose capacity to give adequately informed consent is not impaired;**
- **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 person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,**
- **in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.**

Commentary on Guideline 15

General considerations. Most individuals with mental or behavioural disorders are capable of giving informed consent; this Guideline is concerned only with those who are not capable or who because their condition deteriorates become temporarily incapable. They should never be subjects of research that might equally well be carried out on persons 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. The investigator must obtain the approval of an ethical review committee to include in research persons who by reason of mental or behavioural disorders are not capable of giving informed consent. The willing cooperation of such persons should be sought to the extent that their mental state permits, and any objection on their part to taking part in any study that has no components designed to benefit them directly should always be respected. The objection of such an individual to an investigational intervention intended to be of therapeutic benefit should be respected unless there is no reasonable medical alternative and local law permits overriding the objection. The agreement of an immediate family member or other person with a close personal relationship with the individual should be sought, but it should be recognized that these proxies may have their own interests that may call their permission into question. Some relatives may not be primarily concerned with protecting the rights and welfare of the patients. Moreover, a close family member or friend may wish to take advantage of a research study in the hope that it will succeed in "curing" the condition. Some jurisdictions do not permit third-party permission for subjects lacking capacity to consent.Legal authorization may be necessary to involve in research an individual who has been committed to an institution by a court order.

Serious illness in persons who because of mental or behavioural disorders are unable to give adequately informed consent. Persons who because of mental or behavioural disorders are unable to give adequately informed consent and 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.

Persons who are unable to give adequately informed consent by reason of mental or behavioural disorders are, in general, not suitable for participation in formal clinical trials except those trials that are designed to be responsive to their particular health needs and can be carried out only with them.

(See also Guidelines 8: *Benefits and risks of study participation;* 9: *Special limitations on risks when subjects are not capable of giving consent;* and 13: *Research involving vulnerable persons*.)

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

Commentary on Guideline 16

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 medical 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.

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. 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 if they become pregnant during the research.

Although this general presumption favours the inclusion of women in research, it must be acknowledged that in some parts of the world women are vulnerable to neglect or harm in research because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering. When women in such situations are potential subjects in research, investigators need to exercise special care in the informed consent process to ensure that they have adequate time and a proper environment in which to take decisions on the basis of clearly given information.

Individual consent of women: In research involving women of reproductive age, whether pregnant or

non-pregnant, only the informed consent of the woman herself is required for her participation. In no case should the permission of a spouse or partner replace the requirement of individual informed consent. If women wish to consult with their husbands or partners or seek voluntarily to obtain their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable. A strict requirement of authorization of spouse or partner, however, violates the substantive principle of respect for persons.

A thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. For women who are not pregnant at the outset of a study but who might become pregnant while they are still subjects, the consent discussion should include information about the alternative of voluntarily withdrawing from the study and, where legally permissible, terminating the pregnancy. Also, if the pregnancy is not terminated, they should be guaranteed a medical follow-up.

Guideline 17: Pregnant women as research participants.

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.

Research in this population should be performed only if it is relevant

to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity .

Commentary on Guideline 17

The justification of research involving pregnant women is complicated by the fact that it may present risks and potential benefits to two beings – the woman and the fetus – as well as to the person the fetus is destined to become. Though the decision about acceptability of risk should be made by the mother as part of the informed consent process, it is desirable in research directed at the health of the fetus to obtain the father´s opinion also, when possible. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the fetus should be made by the woman as part of the informed consent process.

Especially in communities or societies in which cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate, or not to participate, in research. Special safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus. Where fetal abnormality is not recognized as an indication for abortion, pregnant women should not be recruited for research in which there is a realistic basis for concern that fetal abnormality may occur as a consequence of participation as a subject in research.

Investigators should include in protocols on research on pregnant women a plan for monitoring the

outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

Guideline 18: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Commentary on Guideline 18

Confidentiality between investigator and subject. Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means. During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality.

Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Drug regulatory authorities have the right to inspect clinical-trial records, and a sponsor`s clinical-compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects**.**

Participation in HIV/AIDS drug and vaccine trials may impose upon the research subjects significant associated risks of social discrimination or harm; such risks merit consideration equal to that given to adverse medical consequences of the drugs and vaccines. Efforts must be made to reduce their likelihood and severity. For example, subjects 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 them with documents attesting to their participation in vaccine trials, or by maintaining a confidential register of trial subjects, from which information can be made available to outside agencies at a subject's request.

Confidentiality between physician and patient. Patients have the right to expect that their physicians and other health-care professionals will hold all information about them in strict confidence and disclose it only to those who need, or have a legal right to, the information, such as other attending physicians, nurses**,** or other health-care workers who perform tasks related to the diagnosis and treatment of patients. A treating physician should not disclose any identifying information about patients to an investigator unless each patient has given consent to such disclosure and unless an ethical review committee has approved such disclosure.

Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiological studies often make use of such records. For such studies it

is usually impracticable to obtain the informed consent of each identifiable patient; an ethical review committee may waive the requirement for informed consent when this is consistent with the requirements of applicable law and provided that there are secure safeguards of confidentiality. (See also Guideline 4 Commentary: *Waiver of the consent requirement.)* In institutions in which records may be used for research purposes without the informed consent of patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement in patient-information brochures. For research limited to patients' medical records, access must be approved or cleared by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

Issues of confidentiality in genetic research. An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process.

When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject`s physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labelled.

Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects` consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects`consent; such plans should be clearly explained during the process of obtaining informed consent.

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Commentary on Guideline 19

Guideline 19 is concerned with two distinct but closely related entitlements. The first is the

uncontroversial entitlement to free medical treatment and compensation for accidental injury inflicted by procedures or interventions performed exclusively to accomplish the purposes of research (non-therapeutic procedures). The second is the entitlement of dependants to material compensation for death or disability occurring as a direct result of study participation. Implementing a compensation system for research-related injuries or death is likely to be complex, however.

Equitable compensation and free medical treatment. Compensation is owed to research subjects who are disabled as a consequence of injury from procedures performed solely to accomplish the purposes of research. Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice. In the early stages of drug testing (Phase I and early Phase II), it is generally unreasonable to assume that an investigational drug holds out the prospect of direct benefit for the individual subject; accordingly, compensation is usually owed to individuals who become disabled as a result of serving as subjects in such studies.

The ethical review committee should determine in advance: i) the injuries for which subjects will receive free treatment and, in case of impairment, disability or handicap resulting from such injuries, be compensated; and ii) the injuries for which they will not be compensated. Prospective subjects should be informed of the committee's decisions, as part of the process of informed consent. As an ethical review committee cannot make such advance determination in respect of unexpected or unforeseen adverse reactions, such reactions must be presumed compensable and should be reported to the committee for prompt review as they occur.

Subjects must not be asked to waive their rights to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or 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 right to seek compensation for impairment, disability or handicap. Prospective subjects should be informed that they will not need to take legal action to secure the free medical treatment or compensation for injury to which they may be entitled. They should also be told what medical service or organization or individual will provide the medical treatment and what organization will be responsible for providing compensation.

Obligation of the sponsor with regard to compensation. Before the research begins, the sponsor, whether a pharmaceutical company or other organization or institution, or a government (where government insurance is not precluded by law), should agree to provide compensation for any physical injury for which subjects are entitled to compensation, or come to an agreement with the investigator concerning the circumstances in which the investigator must rely on his or her own insurance coverage (for example, for negligence or failure of the investigator to follow the protocol, or where government insurance coverage is limited to negligence). In certain circumstances it may be advisable to follow both courses. Sponsors should seek adequate insurance against risks to cover compensation, independent of proof of fault.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.

Capacity-building may include, but is not limited to, the following activities:

- **establishing and strengthening independent and competent ethical review processes/ committees**
- **strengthening research capacity**
- **developing technologies appropriate to health-care and biomedical research**
- **training of research and health-care staff**
- **educating the community from which research subjects will be drawn**

Commentary on Guideline 20

External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research. Before undertaking research in a host country with little or no such capacity, external sponsors and investigators should include in the research protocol a plan that specifies the contribution they will make. The amount of capacity building reasonably expected should be proportional to the magnitude of the research project. A brief epidemiological study involving only review of medical records, for example, would entail relatively little, if any, such development, whereas a considerable contribution is to be expected of an external sponsor of, for instance, a large-scale vaccine field-trial expected to last two or three years.

The specific capacity-building objectives should be determined and achieved through dialogue and negotiation between external sponsors and host-country authorities. External sponsors would be expected to employ and, if necessary, train local individuals to function as investigators, research assistants or data managers, for example, and to provide, as necessary, reasonable amounts of financial, educational and other assistance for capacity-building. To avoid conflict of interest and safeguard the independence of review committees, financial assistance should not be provided directly to them; rather, funds should be made available to appropriate authorities in the host-country government or to the host research institution.

(See also Guideline 10: *Research in populations and communities with limited resources*)

Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

– health-care services that are essential to the safe conduct of the research;

– treatment for subjects who suffer injury as a consequence of research interventions; and,

– services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

Commentary on Guideline 21

Obligations of external sponsors to provide health-care services will vary with the circumstances of particular studies and the needs of host countries. The sponsors' obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long. The details of these arrangements should be agreed by the sponsor, officials of the host country, other interested parties, and, when appropriate, the community from which subjects are to be drawn. The agreed arrangements should be specified in the consent process and document.

Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.

The obligation to ensure that subjects who suffer injury as a consequence of research interventions obtain medical treatment free of charge, and that compensation be provided for death or disability occurring as a consequence of such injury, is the subject of Guideline 19, on the scope and limits of such obligations.

When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care. In general, also, in the course of a study, sponsors should disclose to the proper health authorities information of public health concern arising from the research.

The obligation of the sponsor to make reasonably available for the benefit of the population or community concerned any intervention or product developed, or knowledge generated, as a result of the research is considered in Guideline 10: *Research in populations and communities with limited resources.*

Appendix 1

Items to be included in a protocol (or associated documents) for biomedical research involving human subjects.

(Include the items relevant to the study/project in question)

1. Title of the study;

2. A summary of the proposed research in lay/non-technical language.

3. A clear statement of the justification for the study, its significance in development and in meeting the needs of the country /population in which the research is carried out;

4. The investigators` views of the ethical issues and considerations raised by the study and, if appropriate, how it is proposed to deal with them;

5. Summary of all previous studies on the topic, including unpublished studies known to the investigators and sponsors, and information on previously published research on the topic, including the nature, extent and relevance of animal studies and other preclinical and clinical studies;

6. A statement that the principles set out in these Guidelines will be implemented;

7. An account of previous submissions of the protocol for ethical review and their outcome;

8. A brief description of the site(s) where the research is to be conducted, including information about the adequacy of facilities for the safe and appropriate conduct of the research, and *relevant* demographic and epidemiological information about the country or region concerned;

9. Name and address of the sponsor;

10. Names, addresses, institutional affiliations, qualifications and experience of the principal investigator and other investigators;

11. The objectives of the trial or study, its hypotheses or research questions, its assumptions, and its variables;

12. A detailed description of the design of the trial or study. In the case of controlled clinical trials the description should include, but not be limited to, whether assignment to treatment groups will be randomized (including the method of randomization), and whether the study will be blinded (single blind, double blind), or open;

13. The number of research subjects needed to achieve the study objective, and how this was

statistically determined;

14. The criteria for inclusion or exclusion of potential subjects, and justification for the exclusion of any groups on the basis of age, sex, social or economic factors, or for other reasons;

15. The justification for involving as research subjects any persons with limited capacity to consent or members of vulnerable social groups, and a description of special measures to minimize risks and discomfort to such subjects;

16. The process of recruitment, e.g., advertisements, and the steps to be taken to protect privacy and confidentiality during recruitment;

17. Description and explanation of all interventions (the method of treatment administration, including route of administration, dose, dose interval and treatment period for investigational and comparator products used);

18. Plans and justification for withdrawing or withholding standard therapies in the course of the research, including any resulting risks to subjects;

19. Any other treatment that may be given or permitted, or contraindicated, during the study;

20. Clinical and laboratory tests and other tests that are to be carried out;

21. Samples of the standardized case-report forms to be used, the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of subjects with the treatment;

22. Rules or criteria according to which subjects may be removed from the study or clinical trial, or (in a multi-centre study) a centre may be discontinued, or the study may be terminated;

23. Methods of recording and reporting adverse events or reactions, and provisions for dealing with complications;

24. The known or foreseen risks of adverse reactions, including the risks attached to each proposed intervention and to any drug, vaccine or procedure to be tested;

25. For research carrying more than minimal risk of physical injury, details of plans, including insurance coverage, to provide treatment for such injury, including the funding of treatment, and to provide compensation for research-related disability or death;

26. Provision for continuing access of subjects to the investigational treatment after the study, indicating its modalities, the individual or organization responsible for paying for it, and for how long it will continue;

27. For research on pregnant women, a plan, if appropriate, for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.

28. The potential benefits of the research to subjects and to others;

29. The expected benefits of the research to the population, including new knowledge that the study

might generate;

30. The means proposed to obtain individual informed consent and the procedure planned to communicate information to prospective subjects, including the name and position of the person responsible for obtaining consent;

31. When a prospective subject is not capable of informed consent, satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative*;*

32. An account of any economic or other inducements or incentives to prospective subjects 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;

33. Plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic, that could affect subjects' willingness to continue in the study;

34. Plans to inform subjects about the results of the study;

35. The provisions for protecting the confidentiality of personal data, and respecting the privacy of subjects, including the precautions that are in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives without the consent of the subject;

36. Information about how the code, if any, for the subjects' identity is established, where it will be kept and when, how and by whom it can be broken in the event of an emergency;

37. Any foreseen further uses of personal data or biological materials;

38. A description of the plans for statistical analysis of the study, including plans for interim analyses, if any, and criteria for prematurely terminating the study as a whole if necessary;

39. Plans for monitoring the continuing safety of drugs or other interventions administered for purposes of the study or trial and, if appropriate, the appointment for this purpose of an independent data-monitoring (data and safety monitoring) committee;

40. A list of the references cited in the protocol;

41. The source and amount of funding of the research: the organization that is sponsoring the research and a detailed account of the sponsor's financial commitments to the research institution, the investigators, the research subjects, and, when relevant, the community;

42. The arrangements for dealing with financial or other conflicts of interest that might affect the judgement of investigators or other research personnel: informing the institutional conflict-of-interest committee of such conflicts of interest; the communication by that committee of the pertinent details of the information to the ethical review committee; and the transmission by that committee to the research subjects of the parts of the information that it decides should be passed on to them;

43. The time schedule for completion of the study;

44. For research that is to be carried out in a developing country or community, the contribution that the sponsor will make to capacity-building for scientific and ethical review and for biomedical research in the host country, and an assurance that the capacity-building objectives are in keeping with the values and expectations of the subjects and their communities;

45. Particularly in the case of an industrial sponsor, a contract stipulating who possesses the right to publish the results of the study, and a mandatory obligation to prepare with, and submit to, the principal investigators the draft of the text reporting the results;

46. In the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority;

47. Circumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people;

48. A statement that any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor to take appropriate action against such unacceptable procedures.

Appendix 2

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

<www.wma.net>

Appendix 3

THE PHASES OF CLINICAL TRIALS OF VACCINES AND DRUGS

Vaccine development

Phase I refers to the first introduction of a candidate vaccine into a human population for initial determination of its safety and biological effects, including immunogenicity. This phase may include studies of dose and route of administration, and usually involves fewer than 100 volunteers.

Phase II refers to the initial trials examining effectiveness in a limited number of volunteers (usually between 200 and 500); the focus of this phase is immunogenicity.

Phase III trials are intended for a more complete assessment of safety and effectiveness in the prevention

of disease, involving a larger number of volunteers in a multicentre adequately controlled study.

Drug development

Phase I refers to the first introduction of a drug into humans. Normal volunteer subjects are usually studied to determine levels of drugs at which toxicity is observed. Such studies are followed by dose-ranging studies in patients for safety and, in some cases, early evidence of effectiveness.

Phase II investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.

Phase III trials are performed after a reasonable probability of effectiveness of a drug has been established and are intended to gather additional evidence of effectiveness for specific indications and more precise definition of drug-related adverse effects. This phase includes both controlled and uncontrolled studies.

Phase IV trials are conducted after the national drug registration authority has approved a drug for distribution or marketing. These trials may include research designed to explore a specific pharmacological effect, to establish the incidence of adverse reactions, or to determine the effects of long-term administration of a drug. Phase IV trials may also be designed to evaluate a drug in a population not studied adequately in the pre-marketing phases (such as children or the elderly) or to establish a new clinical indication for a drug. Such research is to be distinguished from marketing research, sales promotion studies, and routine post-marketing surveillance for adverse drug reactions in that these categories ordinarily need not be reviewed by ethical review committees (see Guideline 2).

The ethics of research related to healthcare in developing countries

a follow-up Discussion Paper

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The ethics of research related to healthcare in developing countries

a follow-up Discussion Paper based on the Workshop held in Cape Town, South Africa 12–14th February 2004

NUFFIELD COUNCIL ON BIOETHICS

Nuffield Council on Bioethics

The terms of reference of the Council are:

1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

The Nuffield Council on Bioethics is funded jointly by
the Medical Research Council, the Nuffield Foundation and the Wellcome Trust

Foreword

There is a bewildering multiplicity of guidelines, regulations, declarations and recommendations on the ethics of research relating to healthcare in developing countries. They tend to be both too general to provide answers to practical problems that arise in the course of research, and too specific in that they fail to take account of differing circumstances in developing countries.

The Nuffield Council on Bioethics co-hosted a very productive Workshop with the Medical Research Council of South Africa in Cape Town in February 2004. The Workshop was a follow-up of the Council's Report on *The ethics of research related to healthcare in developing countries*, published in 2002. The Council was delighted to provide an opportunity for researchers, sponsors and members of ethics committees from developed and developing countries to discuss the themes of our Report, and to consider how the various guidelines are applied in practice. Fifty-eight participants from 28 countries pooled their considerable expertise to discuss and debate the issues. We were able to sponsor delegates to attend the Workshop, with the assistance of the UK Department for International Development, the UK Medical Research Council, the Wellcome Trust and the Rockefeller Foundation. We are grateful to them for their generous support.

It was fitting that this meeting was held on the African continent and was co-hosted with the Medical Research Council of South Africa (MRC), which has been at the forefront of developing ethical standards in clinical research. We are most grateful to colleagues from the MRC for their valuable assistance in organising the Workshop, particularly Mandy Salomo and Deidre Raubenheimer. The Council is, as usual, much indebted to its own staff from the Secretariat for their unstinting efforts to ensure that the Workshop was a success. Particular thanks are due to Nicola Perrin (Public Liaison Manager) for her excellent contribution.

SIR BOB HEPPLE QC FBA
Chairman

Acknowledgements

This Discussion Paper is based on a follow-up Workshop on the ethics of research related to healthcare in developing countries, held in Cape Town from 12–14th February 2004. The Council is very grateful to all the delegates and members of the Steering Committee for their valuable contributions to the Workshop and for their comments on earlier drafts of the Paper.

Dr Jerry Coovadia, Dr Liza Dawson, Professor Brian Greenwood, Professor Adetokunbo Lucas and Mr Peteris Zilgalvis peer reviewed an earlier version of this Paper and Dr John Williams commented on Chapter 6. Ms Shawneequa Callier conducted research for the background paper for the Workshop during an internship at the Council in August 2003. Nicola Perrin organised the Workshop and made a substantial contribution to this Paper. The Council is deeply grateful to them all.

The Council would like to thank the members of the Medical Research Council of South Africa for their help co-hosting the Workshop. Generous support from the UK Department for International Development (DFID), the UK Medical Research Council, the Wellcome Trust and the Rockefeller Foundation is gratefully acknowledged.

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Table of contents

Executive Summary

Many people in the developing world suffer from poor health and reduced life expectancy. The role of research that contributes to the development of appropriate treatments and disease prevention measures is vital. However, lack of resources and weak infrastructure mean that many researchers in developing countries have very limited capacity to conduct their own clinical research. They therefore often undertake research in partnership with groups from developed countries. A sound ethical framework is a crucial safeguard to avoid possible exploitation of research participants in these circumstances.

Much attention has been given to providing guidance which addresses ethical issues raised by externally sponsored healthcare-related research in developing countries. A number of international organisations have recently revised existing guidelines or prepared new ones (see paragraphs 1.9–1.15 and Appendix A). The Council held a Workshop, co-hosted with the Medical Research Council (MRC) of South Africa, in February 2004 to explore the practical implications of new and recently revised guidelines since the publication of the Council's 2002 Report.[1] This Paper reports the discussions of four topics at the Workshop: consent, standards of care, what happens after the research is over, and ethical review.

Delegates emphasised that applying guidance in practice is often fraught with difficulty. When the different guidelines are compared, they are markedly inconsistent in some areas. The guidelines vary with regard to the scope and level of detail of information to be provided in the consent process (paragraphs 2.9–2.16), the obligation to provide a universal standard of care to control groups (paragraphs 3.6–3.10), the use of placebos (paragraphs 3.11–3.15), and the extent to which research participants are owed access to successful therapeutics after research is complete (paragraphs 4.4–4.17). There is also variation in relation to the degree of involvement of the host country in the review process (paragraphs 5.8–5.15).

Furthermore, some of the guidelines establish standards that are inappropriate for the developing country setting. A number of case studies provided by delegates illustrate difficulties which have arisen. These include obtaining consent in emergency settings (paragraph 2.7), providing the universal standard of care for control groups in vaccine trials (Box 3.2), and securing guarantees from sponsors or physicians that access to successful therapeutics will be provided to participants once a trial is over (paragraph 4.12). Faithful adherence to some of the provisions within the guidelines is often unachievable. Moreover, despite attempts at clarification, the status of pre-eminent guidelines such as the Declaration of Helsinki, is viewed by some as merely aspirational and by others as akin to regulation. The possibility that researchers may forgo conducting valuable research in developing countries because sponsors in developed countries or review committees in sponsor countries may judge it incompatible with specific provisions of guidance continues to be a cause for concern (paragraphs 6.26–6.34).

Researchers, sponsors and members of ethical review committees must judge for themselves how to approach some of these complex issues. In some countries they will be assisted by national guidance that takes account of local needs and the cultural context. Aligning externally sponsored research with national research priorities (paragraphs 6.22–6.25), and initiating early discussion of the issues with national authorities as well as the local communities concerned, will provide researchers with a crucial counterbalance to the generalised and sometimes unsatisfactory framework of international guidance. The existence of independent research ethics committees is crucial in achieving this aim (paragraphs 5.1–5.24).

Continued

1 Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries* (London: NCOB).

The Paper draws together some of the general themes that were discussed during the meeting, including community participation, the development of expertise, sustainability, partnership and ensuring feedback from research (paragraphs 6.2–6.12). Issues requiring further discussion are also identified, including those raised by chronic diseases, research on public health, and intellectual property (paragraphs 6.13–6.21).

Chapter 1

Introduction

Introduction

Background

1.1 Research is urgently needed to help to address the burden of disease that affects the developing world. The ability of researchers in poor countries to conduct their own clinical studies is severely impeded by limited funds and a lack of trained staff. Socio-economic factors are also influential. For example, opportunities in education and research, the integrity of family life and the quality of national and local governance all play a part. It is vital therefore that developed countries should help to establish partnerships, involving both the public and the private sector, to conceptualise, design, implement, fund and assess healthcare-related research in developing countries. However, the inequalities that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out.

1.2 Several of the issues raised by externally sponsored research, such as the standard of care provided to research participants, are not confined to developing countries. They tend, however, to be exacerbated in situations where provision of basic healthcare is limited, and where research ethics committees are under-resourced or even absent, as is often the case in developing countries. In addition, researchers are faced with diverse and sometimes conflicting guidance as to what may be ethically appropriate.

1.3 International guidelines to protect participants in biomedical research have been in place for several decades. Specific guidelines on the ethics of healthcare-related research have recently been revised by a number of international bodies, including the World Medical Association (WMA), and the Council for International Organizations of Medical Sciences (CIOMS). New guidelines have been prepared by the European Group on Ethics in Science and New Technologies (EGE) and the Council of Europe's Steering Committee on Bioethics (CDBI) (see paragraphs 1.9–1.14 and Table 1.1). The reasoned application of the available guidelines in the light of ethical principles is a primary aim of ethical review of research proposals. However, variation in the guidelines provided by these different bodies means that the resolution of complex issues raised by research in developing countries continues to be challenging.

1.4 In 2002, the Nuffield Council on Bioethics published the Report, *The ethics of research related to healthcare in developing countries*. It concluded that externally funded research in developing countries is crucial but must be subject to rigorous ethical safeguards to prevent the exploitation of those who take part. Rather than setting out guidelines, the Report provides an ethical framework for those designing or conducting externally sponsored research in the developing world.

1.5 The Council held a follow-up Workshop in February 2004, co-hosted with the Medical Research Council (MRC) of South Africa, to explore the practical implications of new and recently revised guidelines since the publication of the 2002 Report. The Workshop provided an opportunity for researchers, sponsors and members of ethics committees from developed and developing countries to exchange experiences, and to consider how the guidelines may be applied in practice, particularly when they provide conflicting advice. Fifty-eight delegates from 28 countries attended the meeting. Further details about the Workshop, the programme and a list of delegates can be found in Appendix C.

1.6 This Discussion Paper identifies areas of concern arising from recent developments in the guidelines and draws out general themes from the discussion. It does not reconsider specific ethical issues addressed in the 2002 Report. Some background knowledge of the issues related to research in developing countries is assumed; a bibliography for those new to the issues is given in Appendix D.

Structure of the Paper

1.7 This Paper begins with a brief overview of a number of guidelines, regulations, declarations and recommendations that have been newly established or revised since 2002 (see Table 1.1). Most are only persuasive and do not have the force of law. We refer to them collectively as 'the guidance'. Chapters 2–5 report the discussion of four topics at the Workshop: consent, standards of care, what happens after the research is over, and ethical review. These topics are often interrelated, but are treated separately here for ease of reference. Each chapter starts with a summary of relevant guidance that highlights areas of agreement and disagreement, and then provides details of the participants' own experiences and concerns raised during the Workshop.

1.8 Chapter 6 was drafted by the Steering Committee following discussion at the Workshop. It draws together some of the general themes that were identified during the meeting, including community participation, the development of expertise, sustainability, partnership and ensuring feedback from research. Issues requiring further discussion are also identified, including those raised by chronic diseases, research on public health, and intellectual property. A discussion of the importance of defining research priorities follows. Finally, in light of the discussion at the Workshop, we consider the status of the Declaration of Helsinki, and its practical implementation. It should be noted that not all of the views reported in the Paper were necessarily shared by all of the delegates or the Nuffield Council.

Overview of the guidance

1.9 When planning research in developing countries, researchers and sponsors may have to refer to:

- international guidelines or conventions;
- European Union Directives;
- national laws or guidelines;
- regulations and guidelines for research sponsored by the pharmaceutical industry;
- guidelines produced by funding agencies;
- institutional guidelines;
- guidelines relating to a specific disease; and
- recommendations from advisory bodies.

1.10 Since it was first published in 1964, the Declaration of Helsinki has been regarded by many as the pre-eminent guidance on the ethics of research related to healthcare. The Declaration established a set of fundamental principles from which were derived some general rules of conduct for research. Since 1964, it has been revised five times by the WMA, most recently in 2000 (WMA 2000). Paragraphs 29 (standards of care) and 30 (after the research is over) were discussed and clarified in 2002 and 2004 respectively (see Box 4.1).

1.11 In 1982, CIOMS, in collaboration with the WHO, published guidelines to address the special circumstances that arise when applying the Declaration of Helsinki to research undertaken in developing countries. The CIOMS guidelines were revised in 1991, 1993 and in 2002. EU 2001, EGE 2003, and CoE 2004 have all been established relatively recently.

1.12 An additional set of regulations and guidelines are in place to provide technical standards for research sponsored by the pharmaceutical industry. For example, the International Conference on Harmonisation (ICH) *Harmonised Tripartite Guidelines: Guideline on Good*

Table 1.1: Guidance considered in the Paper [1]

Guidance	Status	Abbreviations in Paper
World Medical Association (WMA): *Declaration of Helsinki* as last revised in Oct 2000; Note of Clarification on Paragraph 29, Dec 2002; Workgroup Report on the revision of Paragraph 30, Sep 2003; and Note of Clarification on Paragraph 30, October 2004.	Not legally binding, but referred to in other forms of guidance and regulation	WMA 2000
The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the **World Health Organization (WHO):** *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* as last revised in Sep 2002.	Not legally binding	CIOMS 2002
Council of Europe (CoE): *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research*, prepared by the Steering Committee on Bioethics (CDBI) of the Council of Europe adopted by the Committee of Ministers, June 2004. (A draft Protocol, approved by the CDBI in June 2003, was discussed during the Workshop in February 2004.)	Legally binding (if signed and ratified)[2]	CoE 2004
European Council and European Parliament (Eurpean Union): *Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, April 2001, adopted by Member States by May 2003, brought into force May 2004.	Incorporated into national law for EU Member States; applies within the EU and for multi-centre clinical trials taking place in Member States and other countries	EU 2001

Continued

1 Discussion at the Workshop and in this Paper considers guidance that has been newly established or revised since 2002. Some of these documents have been finalised since the Workshop, for example WMA 2000, paragraph 30 and CoE 2004. In these cases, the draft versions were referred to at the meeting. In this Paper, we refer to the final versions, which for our purpose, do not differ significantly from the draft documents.

2 The Protocol is only binding for those countries that have signed and ratified it, and are party to the 1997 *Convention on Human Rights and Biomedicine*. Nineteen countries have signed and ratified the Convention thus far: Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Georgia, Greece, Hungary, Iceland, Lithuania, Moldova, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain and Turkey. The Council of Europe includes all members of the EU in its membership as well as other non-EU European countries.

Table 1.1: Guidance considered in the Paper *(Continued)*

Guidance	Status	Abbreviations in Paper
The European Group on Ethics in Science and New Technologies (EGE): *Opinion Nr 17 on the ethical aspects of clinical research in developing countries*, published in Jan 2003.	Advisory	EGE 2003
Nuffield Council on Bioethics: *The ethics of research related to healthcare in developing countries*, April 2002.[3]	Advisory	NCOB 2002

Clinical Practice (1996) provides unified technical standards for clinical trials so that clinical data are mutually acceptable to regulatory authorities in the EU, US and Japan.[4]

1.13 Some organisations have devised their own guidelines to address ethical issues raised by research in developing countries, or related to a specific disease. For example, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has published guidelines for researchers conducting research on vaccines for HIV/AIDS.[5] Funding agencies, including the UK Medical Research Council (MRC), the Wellcome Trust and the National Institutes of Health (NIH), that sponsor healthcare-related research in developing countries have also produced guidelines for researchers.[6]

1.14 In recent years, some of the guidelines listed in Table 1.1 have been criticised. Critics argue that they are too general to address many of the specific and often controversial issues that are raised by research. For example, guidelines about the standards of care that should be provided to those participating in clinical trials, and the level of medical care that should be provided after a trial is over tend to be set out in very general terms and have been subject to varied and contradictory interpretations.[7] Furthermore, these guidelines are not consistent in the advice that is given. Nor do they always take into account the special circumstances that may attend externally funded research undertaken in developing countries.

3 Whereas the other documents listed in Table 1.1 provide specific guidelines on externally sponsored research, this Report focuses on establishing an ethical framework for those conducting such research, and provides recommendations.

4 ICH is a project that brings together the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. See also ICH (1997) *Technical Requirements for Registration of Pharmaceuticals for Human Use, and WHO (1995) Guidance on Good Clinical Practice for Trials on Pharmaceutical Products*.

5 UNAIDS (2000) *Ethical Considerations in HIV Preventive Vaccine Research* (Geneva: UNAIDS).

6 Medical Research Council UK (2004) *MRC Ethics Guide: Research involving human participants in developing societies* (London: MRC); Wellcome Trust (2005) *Wellcome Trust Funded Research Involving People Living in Developing Countries* (London: Wellcome Trust); NIH (1997) *Guidelines for the conduct of research involving human subjects at the NIH* (5th Printing August 2004) (Washington, DC: NIH). The NIH guidelines apply to research sponsored from within the US but carried out elsewhere. See also National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical trials in developing countries* (Bethesda: NBAC), which was published prior to the Report of the Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*.

7 NCOB 2002, paragraphs 5.3–5.4.

1.15 Despite these difficulties, the consideration of suitable guidance and a rigorous process of ethical review can help those designing or conducting research to address the issues that are raised. However, even the best possible guidance would not necessarily resolve them. In the following chapters, we discuss applications of the guidance listed in Table 1.1, and the problems that may be encountered in four important areas for healthcare-related research: consent, standards of care, what happens after the research is over, and ethical review. In each chapter, the issues are first examined in the light of international guidance, and secondly, in the context of discussions at the Workshop. Tables comparing relevant provisions of the guidance, based on a Background Paper that was circulated to all Workshop delegates, are provided at Appendix A.

Chapter 2

Consent

Consent

Introduction

2.1 The importance of obtaining informed consent from individuals who take part in research has been widely recognised. Individuals giving consent must be informed of the potential risks and benefits of participating in research. If they take part, they must do so voluntarily. In the case of research involving minors or individuals without the mental capacity to consent, consent can be given by a person authorised to do so on their behalf. When externally sponsored research is conducted in developing countries, a range of additional issues may arise when consent is sought from potential participants. For example, in some communities it is customary for male members of the family to make decisions on behalf of wives and children. There will often be a tension between the duty of the researcher to be sensitive to cultural differences, and the duty to ensure that each individual has consented to participate in research.

2.2 The way in which information on the potential risks and benefits of research is provided is particularly important when participants are from developing countries. Those approached to participate may lack familiarity with basic practices of medical research, such as the use of clinical trials to test new treatments. Views about the causation of illness may differ from the 'western' medical model. Researchers must do their best to communicate information accurately and in an intelligible and appropriate way, taking account of local knowledge and beliefs. There are also questions about the type of documentation that is suitable for use in communities where many lack literacy. In such situations, it may be inappropriate to ask participants to sign consent forms. Witnessed verbal consent might be used instead.

2.3 Participants in research are likely to have a range of motivations for taking part. In developing countries some may agree to participate because they believe it may be their only means of receiving improved healthcare or other benefits. There is a potential conflict between the dual roles of healthcare practitioners who simultaneously provide healthcare and recruit research participants. The process of gaining informed consent must therefore be carefully designed.[1]

2.4 In the Workshop, four issues were considered:

- who should give consent?
- provision of information;
- recording consent; and
- inducements to take part in research.

Who should give consent?

Guidance

2.5 There is general consensus in the guidance that, in the majority of cases, informed consent must be obtained from potential research participants.[2] In addition to individual consent, some guidance (CIOMS 2002, EGE 2003 and NCOB 2002) also requires investigators to respect cultural traditions by consulting the community or 'senior family members' when

1 For further information about consent and the ethics of healthcare-related research see NCOB 2002, Chapter 6.

2 Exceptions to the general requirement for informed consent include epidemiological research activities that entail monitoring for public health by using, for example, surplus human tissue.

appropriate[3] (see Appendix A, Table 1). Such 'community consent' may be crucial in specific cases, although the guidance is unanimous that it must be in addition to, rather than instead of, properly informed individual consent.

Workshop discussion

2.6 During discussion, delegates reaffirmed that where community consent was sought, it should be in addition to genuine, voluntary consent by individuals (see Box 2.1).[4] Community consent could have several purposes. It could be used as a form of consultation with the community before individuals are approached, as a method of obtaining 'permission' from leaders, and as an additional means of providing information. Indeed, consultation with the community as a complementary activity was often likely to be crucial. Understanding the social and cultural context in which research was being conducted was essential, and involving the community demonstrated respect for local traditions. In addition, it was suggested that, on many occasions, informing and consulting with the community had been proved to be the most effective means of aiding understanding and helping to ensure that consent was genuine. (See paragraphs 2.9–2.16 for further discussion about the provision of information for informed consent.)

Box 2.1: **Genuine consent**

The concept of 'genuine consent' was introduced by the Council in 1995 in the Report *Human tissue: ethical and legal issues*. In this Report, the Council concluded that 'the ethically significant requirement is not that consent be complete, but that it be genuine' (paragraph 6.20). This concept was further discussed in NCOB 2002 (paragraphs 6.4–6.8). Since description can never be fully exhaustive, consent will always be an action that is incompletely described; moreover the descriptions given may often be incompletely understood. This incompleteness cannot be remedied by devising more elaborate consent forms. Fully informed consent is therefore an unattainable ideal. Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers or relatives can understand about procedures and risks, and to react to the limits of their understanding, and of their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent. Ensuring that consent is genuine requires care in detecting and eliminating lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what is proposed, lack of disclosure of material facts or conflicts of interest.

2.7 However, it was observed that in practice, obtaining consent was often not straightforward. Researchers had experienced a range of problems which could not be resolved by recourse to current guidance. One such example involved a clinical trial of anti-malarial treatment in Malawi (see Box 2.2). Treatment of patients with acute disease in a hospital-based trial had raised particular difficulties. The need for immediate treatment meant that there was often little opportunity to discuss research with potential participants and to give them adequate time for reflection before seeking consent. The patient or guardian might also be very distressed. It was suggested that in these circumstances, consent forms must be particularly clear and brief, and that it might be helpful to continue to provide information after emergency care had been initiated. It was suggested that provision of information before a trial started would enable the community to be involved, and allow potential participants to consider the issues in

3 CIOMS 2002, Commentary on Guideline 4; EGE 2003, paragraph 2.7; NCOB, paragraph 6.22.

4 See also NCOB 2002, p77 Box 6.4.

advance (see paragraph 2.14). However, it was often difficult to consult with the relevant community, which might include the entire catchment area of a hospital. This approach would involve contacting large numbers of villages in an area near a hospital, which would be impractical and require significant resources that were unlikely to be available.

Box 2.2: **Difficulties in obtaining consent in emergency situations – clinical trial of antimalarial treatment (case study contributed by Professor Malcolm Molyneux)**

In Malawian villages, many children die of malaria without even reaching hospital. This is due partly to a lack of sophisticated equipment to treat children who are unconscious or unable to drink, and partly to a lack of transport to take patients to a health facility where appropriate treatment could be provided.

A research study was designed to determine whether the use of artesunate suppositories could provide immediate initial treatment for children suspected to have severe malaria, before they were transported to a larger health facility. Artesunate suppositories could be easily stored and administered by unskilled people without sophisticated equipment.

An initial trial was conducted in Blantyre to test whether artesunate was adequately absorbed from the rectum in children with severe malaria. The study, which was conducted in a hospital, involved children admitted with 'moderately severe' malaria. Parental consent was sought for eligible children. Of those enrolled in the trial, four in five received rectal artesunate, and a small control group were given the standard intravenous therapy (quinine).

The process of obtaining consent was not straightforward. The consent form was very complex, with two full pages of text. Researchers found that it was unrealistic to aim to convey this amount of information to a mother with a semi-conscious child. In addition, treatment needed to begin promptly, which meant that the time for explanation, reflection and consultation was limited. Although consent was taken by a nurse in the patient's language, there was also a problem with translation and interpretation of terms such as 'randomisation' and 'drug absorption'.

See Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M and Molyneux ME (2004) Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study *Lancet* **363**:1598-605.

2.8 Other points that were made when considering who should give consent included:

- Particular safeguards may be needed when consent is requested for children (see Boxes 2.2 and 2.3), the mentally incapacitated, and those who are unconscious.
- Obtaining consent in large-scale emergency situations where rapid intervention is required may also be difficult. Examples included situations where research had been conducted on patients with acute disease in refugee camps or during major epidemics. Undertaking a trial of a medicine during a major epidemic of cerebrospinal meningitis was one such case.
- Community randomised trials may raise different issues. For example, in an evaluative study, a new treatment is sometimes made available in health centres in selected communities, and its effects are compared with those in communities not given access to the treatment. In such circumstances it would be important and appropriate to seek the consent of the communities to be included in such a study before decisions are made about which health centres should be included in the trial. While it is clearly appropriate to seek individual informed consent from those offered the new treatment in the communities in which it was introduced (those refusing would be offered the standard treatment), it is unclear whether individuals should be asked to give informed consent in

the communities in which the new treatment was not made available.

- CIOMS 2002 is the only guidance to explicitly allow for the possibility of waiving the process of obtaining consent, when the research carries no more than a minimal risk, and the procedures involved do not usually require signed consent forms.[5] Delegates considered that waiving of consent should only be considered in exceptional circumstances.

Box 2.3: **Consent for children – HIV vaccine trials (case study contributed by Ms Catherine Slack)**

HIV vaccine trials in South Africa (SA) currently involve adults who are able to give consent for participation. However, in some situations there is also a high risk of infection for children. Trials to provide data on safety, immunogenicity and efficacy of preventive HIV vaccines among children are therefore required and issues of consent for children to take part need to be addressed.

Current SA Medical Research Council (MRC) Guidelines allow parents to give consent for their children to participate in research classified as 'non-therapeutic' only where it is observational and of 'negligible' risk.* It is likely that early trials of HIV vaccines will be seen as non-therapeutic but unlikely that HIV vaccine research would fulfil criteria for observational research of negligible risk. Current MRC Guidelines therefore run the risk of excluding children from such trials.

New guidance has therefore been drafted in specific SA MRC Guidelines on HIV vaccine research.† This allows adults to consent to the participation of children in research provided that:

- the research could not be carried out with less vulnerable participants in the trial;
- the purpose is to obtain knowledge relevant to the health needs of children;
- the risks from procedures that do not hold out direct health-related benefit are comparable to those from routine medical or psychological tests;
- the risks from procedures that do hold out direct health-related benefit are justified by the benefit; and
- legal and ethical requirements for consent and assent are met.

* Medical Research Council of South Africa (2002) *Book 1 Guidelines on ethics for medical research: General principles* (SA MRC).

† Medical Research Council of South Africa *Book 5 Guidelines on ethics for medical research: HIV vaccine trials* (SA MRC).

Provision of information

Guidance

2.9 There is unanimous agreement in the guidance that each research participant must be adequately informed about the 'nature, significance, implications and risks' associated with a research trial[6] (Appendix A, Table 1). However, the guidelines vary in the degree of detail that they recommend should be provided to participants. CIOMS 2002 provides the most comprehensive advice. Guideline 5 lists 26 essential features of the research that must be

5 CIOMS 2002, Guideline 4.

6 WMA 2000, paragraph 22; CIOMS 2002, Guideline 4; CoE 2004, Article 14; EU 2001, Article 3, 2(d); EGE 2003, paragraph 2.7; and NCOB 2002, paragraph 6.22.

addressed during the consent process, including the design of the research (e.g. randomisation, double blinding); possible health risks for participants and treatment options; issues relating to data protection; and questions of liability in the case of disability or death resulting from injury related to the research (see also Box 2.4).

2.10 While the provisions of most guidelines focus on issues relating to recording consent, some explanatory notes emphasise the significance of the consent process itself.[7] They stress the importance of developing methods to help participants understand the implications of taking part in research (see Box 2.1).

Workshop discussion

2.11 Several delegates commented that consent forms often appeared to be designed to protect researchers and their sponsors rather than participants. The forms were frequently too long and complex, making them inaccessible to participants. Examples included a consent form for trials of a rotavirus vaccine in India which was nine pages in length. Although the form had been translated into the local language, its content was considered to be too technical for participants to understand. Many potential participants remained confused about both the purpose of the vaccine and the trial. In another example, a consent form for a trial of a meningococcal vaccine in northern Ghana was 14 pages in length. Despite protracted discussion with the sponsors, it had not proved possible to simplify the contents of the form for legal reasons.

2.12 Another problem can arise when consent forms developed for a specific project are adapted without adequate understanding of local knowledge, which may lead to misinterpretation. For example, it was reported that in Kenya a consent form designed in English and translated into the local language was found to have misinterpreted essential information when it was back-translated. Many languages will not have corresponding terms for words such as 'placebo' and particular care is needed if the research is to be explained successfully.

2.13 It was suggested that the essential information for a participant to understand should be identified when a consent form is being drafted. The challenge is to provide clear and concise information which informs the prospective participants without overwhelming or misleading them. Delegates concluded that it was unrealistic to fulfil the 26 requirements for consent set out in the CIOMS guidelines in the consent form itself. Instead, it would be more appropriate to provide a consent form of no more than one page, with essential information contained in a few accessible statements. Additional details could then be provided in an information sheet which would be given to participants to read, or have read to them, at home, before consent was sought. The information in the sheet could also be conveyed to participants in advance of the study through public meetings with the community or by using other methods of explanation, such as illustrations. Some information, relevant only to the ethical review of the study, might be included in the study protocol. A proposal, developed by delegates in the Breakout Groups (see programme, Appendix C) is given in Box 2.4.

7 CIOMS 2002, Commentary on Guideline 4; CoE 2004, Explanatory Report, paragraph 72.

Box 2.4: **Proposal for providing information to prospective research subjects prior to obtaining consent to participate in research**

The 26 CIOMS 2002 requirements for consent are divided below into three groups. They are: those for inclusion in the consent form; those for inclusion in the information sheet, and those for possible inclusion in the research protocol for submission to appropriate research ethics committees (numbers in brackets refer to the list of requirements in CIOMS 2002, Guideline 5 (1-26)).

Information in consent form	Information in additional information sheet	Information in research protocol
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; (2)	for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken; (4)	that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary; (1)
the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care; (3)	whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount; (6)	whether the investigator is serving only as an investigator or as both investigator and the subject's physician; (21)
any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner; (9)	the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it; (5)	the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality; (15)
the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified; (14)	that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status; (7)	
	that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure); (8)	
	any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in	

Continued

Box 2.4: *(Continued)*

Information in consent form	Information in additional information sheet	Information in research protocol
the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care, and details about their storage and possible future use if relevant; (18 and 19)	the research, including risks to the health or well-being of a subject's spouse or partner; (9) (see also *Information in Consent Form*)	
that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, and details about the provision of such treatment; (23)	the direct benefits, if any, expected to result to subjects from participating in the research; (10)	
If relevant: policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject; (16)	the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge; (11)	
	whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them; (12)	
	any currently available alternative interventions or courses of treatment; (13)	
	the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research; (17)	
	whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products; (20)	
	the extent of the investigator's responsibility to provide medical services to the participant; (22)	
	in what way, and by what organization, the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation); (24)	

Continued

Box 2.4: *(Continued)*

Information in consent form	Information in additional information sheet	Information in research protocol
	whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed; (25) that an ethical review committee has approved or cleared the research protocol. (26)	

Summary

A consent form should contain the following information:

I consent to take part in … .

I understand that I am free to withdraw from the research at any time without penalty (2)

It has been explained to me that the purpose of the research is… (3)

And that the risks involved are…. (9)

I understand that the confidentiality of my records will be maintained by … (14)

It has been explained to me what will happen in the event of injury or complications (23)

I have had the opportunity to ask questions

If appropriate: The policy with regard to the use of genetic tests has been explained to me (16)

I understand that x, y and z will happen to any biological samples collected during the course of the research (18, 19, and 20).

2.14 Creative and cost-effective methods of communication may also be required. Communities could be made aware in advance, by using the press, radio and television, by making 'information packs' available, or by holding community seminars. Other examples cited included the use of dance troupes and school plays to convey information (see also Box 2.5). The process of informing participants should continue after enrolment, allowing time for further explanation, reflection and consultation. It might also be helpful for participants to have the opportunity to discuss the trial on more than one occasion, before making a decision on whether to take part.[8]

2.15 Community leaders and representatives, and individual participants, must be able to trust the process of consent. It was suggested that members of the community, rather than just the principal investigator, could also be involved in the process of obtaining consent. However, other delegates were concerned that this step might lead to community leaders having undue influence over recruitment. Delegates agreed that field workers and assistants needed to be trained so they could respond to questions about the research that may be posed by participants.

2.16 Methods to assess whether participants have properly understood the nature of the research

8 This option would not apply to trials of treatment for acute life-threatening illness.

Box 2.5: **Obtaining informed consent – Kenya AIDS Vaccine Initiative (KAVI) (case study contributed by Dr Job Bwayo)**

Trials to evaluate the safety and immunogenicity of a candidate HIV vaccine were held for the first time in Kenya in 2000. The recruitment rate was initially slow and so measures were put in place to improve awareness of the trials in the community. They included:

- Community representatives were given training to enable them to initiate discussions about the purpose, benefits and risks of the research.
- A range of informal community seminars were held. Scientists were invited to 'talk science' to the community in a language that was well understood.
- Interested individuals were invited to attend formal seminars at an evaluation unit, which included the opportunity to participate in question and answer sessions with the researchers.

Measures were also put in place to help ensure that those who were interested in participating had understood the nature of the research:

- Those who wanted to join the trial attended at least three one-to-one counselling sessions before being considered for entry.
- Before potential volunteers were entered into the trial, they took a test to assess their understanding. A minimum score of 80% was required before an individual could be invited to consent to participate.
- Eligible volunteers were given the option to proceed to enrolment or to withdraw their consent, either at this stage or at any other time during the research.

The involvement of the community improved the recruitment of volunteers and the rate of retention. It also enhanced community ownership of the process of vaccine development.

Wakasiaka S, Bwayo JJ, Ndinya JA, Jaoko WG, Omu A, Omosa G M, Ogutu HA and Nyange J (2004) Enhanced volunteer recruitment in HIV vaccine trials in Kenya *XV International AIDS Conference 11-16 July 2004 Bangkok, Thailand Conference* Abstract number: ThPeA6999. Available: http://www.iasociety.org/ejias/show.asp?abstract_id=2170240 Accessed on: 25 Feb 2005.

in which they are participating were also considered. It was suggested that a separate team, again appropriately trained, may be required to monitor consent. Monitoring should aim to assess the participants' general understanding of the implications of the trial rather than test their retention of information with a check list of facts. It was noted that monitoring would be a valuable addition to many trials conducted in developed countries, where participants may have an incomplete understanding of the implications of their participation.

Recording consent

Guidance

2.17 The guidance differs with respect to the acceptability of different methods of documenting consent to participate in research (Appendix A, Table 1). EGE 2003 does not indicate how consent should be recorded, while WMA 2000, CIOMS 2002, CoE 2004 and NCOB 2002 recommend that researchers should obtain written consent when appropriate. When written consent is not feasible, WMA 2000, CIOMS 2002, CoE 2004, EU 2001 and NCOB 2002 state that verbal consent is acceptable, provided that it is formally documented and witnessed.[9] EU 2001 specifies illiteracy as a necessary condition for permitting verbal consent.

9 WMA 2000, paragraph 22; CIOMS 2002, Commentary on Guideline 4; CoE 2004, Explanatory Report, paragraph 79; EU 2001, Article 3.2 d; NCOB 2002, paragraphs 6.37–6.40.

Workshop discussion

2.18 It was suggested that there is too much emphasis on 'written' consent in the guidance. For example, in Mexico, national regulations specify that 'valid informed consent' must be obtained before research begins and that the consent form must be signed by the participant and two witnesses.[10] Researchers have found that this requirement creates some difficulties. The presence of additional people during the consent process may cause discomfort for the participant and limit confidentiality. One of the witnesses will often be the study co-ordinator, but providing a second witness may be more difficult. Investigators will often ask participants to attend with a relative, who can act as a witness and support the participant during the research. However, when the accompanying relative is a man, he may be very influential and inhibit a woman from deciding for herself whether or not to participate. An additional complication is that some sponsors will not accept family members as witnesses.

2.19 There was general agreement that proper monitoring and documentation of the consent process was more important than whether or not a participant provided written consent. If consent is recorded with a tape recorder, it would be important to ensure that the tape was safely stored and would not deteriorate. Delegates agreed that in many situations, having the consent process witnessed would be more acceptable to participants than providing a signature. For example, in Malawi, trial participants were often concerned that signing may entail unforeseen obligations, such as tax liabilities or trouble with the police.

Inducements to take part in research

Guidance

2.20 CIOMS 2002 recommends that payments to research participants, either in money or in kind, 'should not be so large as to persuade them to take undue risks or volunteer against their better judgment'[11] (Appendix A, Table 1). NCOB 2002 comments that inducements to take part in research must be appropriate to the local context and, along with CoE 2004, recommends that they are considered by the local research ethics committee.[12]

Workshop discussion

2.21 Where healthcare facilities are lacking, participants may decide to take part in research in order to have access to better care. The availability of treatment during and after a trial might also count as an inducement. Delegates emphasised that while researchers should aim to ensure that participants are not placed in a worse position by participating in research, a decision to participate must be made voluntarily. Care should be taken to ensure that any payment did not become an inappropriate inducement to accept risks that would not otherwise be considered acceptable. It was suggested that guidance should be clearer on the question of payments, including when they should be made and which costs should be covered. The point at which inducements become excessive was not always clear. In many developing countries, $5 for loss of earnings or for travel costs could be a substantial incentive for individuals to participate. Delegates suggested that, where possible, improvements to healthcare were more appropriate inducements than financial payments (see Box 2.6).

10 Ley General de Salud (General Law of Health) (Articles 100 and 103) *Rules for research in human beings*.

11 CIOMS 2002, Commentary on Guidelines 3 and 7.

12 NCOB 2002, paragraph 6.32; CoE 2004, Articles 11 and 12 and Appendix xvi.

Box 2.6: **Inducements – the International HapMap project (case study contributed by Professor Charles Rotimi)**

An international project, HapMap, was established in 2002 to create a haplotype map of the human genome. The project will describe the common patterns of human DNA sequence variation and may be used to identify genes linked to susceptibilities to disease. Researchers from Canada, China, Japan, Nigeria, the UK and US expect to complete the map by 2005. Participants are asked to donate blood samples so that their DNA can be studied.

Participants in the International HapMap project in Nigeria were each given an equivalent of approximately US $8.00 and multivitamins worth about US $4.00 to compensate them for their time and travel. This amount was comparable to the sum given for the donation of blood (for use in the blood transfusion service) in the same region. Prospective donors were only told that they would be compensated after they had arrived to donate blood. This approach was adopted to guard against the possibility that they would be induced to participate by the prospect of material benefit. However, they might have learned of the payment by word-of-mouth.

One community requested assistance to establish a hospital in return for their contribution to the HapMap project. This request raised concerns that community leaders would place undue pressure on people to participate in the research because of the promise of a new hospital. Even if a hospital was provided for the community, it might not be sustainable in the long term. An alternative healthcare benefit for the local community was therefore under consideration.

See The International HapMap Consortium (2003) The International HapMap Project *Nature* **426**: 789–96; The International HapMap Consortium (2004) Integrating ethics and science in the International HapMap Project *Nature Reviews Genetics* **5**: 467–75.

Summary of discussion on consent

2.22 Several themes emerged during the Workshop. These were:

- The primary purpose of the consent process should be to inform and protect the participant and ensure that he or she understands the reasons for the research and the consequences of taking part.
- This may mean adapting the guidance to fit the local context and will certainly require simple consent forms, supplemented by more detailed information for participants, using appropriate language and explanations.
- It will often be necessary to seek innovative ways of providing information to participants and the process may need to be continued after consent has been given.
- Proper monitoring and documentation of the process is more important than whether the participant provides written consent.
- The trust of the participants in the process is crucial.

2.23 Additional points that are not currently addressed by most guidance included:

- There was some debate as to whether health services and operational research[13] were adequately covered in the guidance. It was suggested that both individual and

[13] Health services and operational research are concerned with the study of methods of delivery of healthcare, access to treatment and quality of care, with the aim of finding improved methods that lead to better care. Such studies often include an evaluation of the cost of providing the intervention and the benefit it provides.

community consent should be sought for this type of research. However, this approach is not currently followed in practice and may be difficult to organise.

- Difficult consent issues had arisen when research was conducted primarily for the benefit of the community rather than for individual participants. For example, a trial might be conducted to find out which treatment would be most appropriately supplied through the local health authority, rather than whether one is better than another.
- Particular difficulties had been experienced when obtaining consent from patients with acute disease in hospitals or in emergency situations.
- The guidance tended to be biased towards clinical trials and did not address issues raised in other areas of research such as genetics.

Chapter 3

Standards of care

Standards of care

Introduction

3.1 There has been significant international debate about the 'standard of care' that should be provided to participants during research in developing countries. Much of the controversy has focused on the level of care provided to the control group in clinical trials. Two questions are fundamental to the debate. First, should the control group receive the best current treatment available anywhere in the world ('universal standard of care'), or treatment based on the standard available in the local or regional context ('non-universal standard of care')? (See Box 3.1 for a summary of these different terms.) Secondly, is it acceptable to give placebos to a control group if an effective treatment already exists but is not available locally?

3.2 Some argue that when research is externally sponsored, participants in developing countries should receive the same standard of care and treatment as participants would receive if the research was conducted in the country of those sponsoring the research. Others argue that the standard of care provided to the control group is a critical component of trial design that affects the scientific value and direction of research (for further discussion see NCOB 2002, p89). They claim that a requirement for a universal standard could prevent research that has the potential to benefit people in developing countries from being undertaken. For example, research which aimed to compare a new treatment with one currently available to the target population might not be possible.

3.3 In 1997, clinical trials designed to determine whether short courses of an antiretroviral treatment (ART) for HIV/AIDS could reduce the transmission of the virus from mother to child were criticised for using placebos, rather than the universal standard of care, in the control groups. Longer courses of the treatment were already known to reduce perinatal transmission of the virus but the trials were conducted in countries where local care did not include access to the medicine. A protracted international debate has not resolved the issue although the some of the guidance has been revised accordingly. The extent of disagreement is reflected in the Background Note to CIOMS 2002, which refers to the 'unresolved or unresolvable conflict' in discussion about the appropriateness of applying a universal standard of care.[1] (See also NCOB 2002, Chapter 7).

3.4 Separate issues that are not addressed in the guidance concern the standard of care that should be provided to research participants who develop either the condition(s) being studied or unrelated conditions. What standard of care should be provided to these participants during, or following, the research period? When research into preventive measures is conducted, what standard of care should be offered to patients who develop the disease once the research is completed? These issues are inter-related but require distinct ethical analysis, since it can be argued that obligations to provide treatment differ in each case. For example, the obligations to provide treatment for patients who develop the disease being studied during the trial can be distinguished from the obligations to provide treatment for unrelated conditions.

3.5 In the Workshop, four main issues were considered:

- the standard of care that should be provided to the control group during research;
- the use of placebos;
- the obligations of sponsors; and
- the provision of care to all trial participants.

[1] CIOMS 2002: The controversy is described in more detail in the Commentary on Guideline 11, which addresses *Choice of control in clinical trials.*

Box 3.1: **Terms used to describe standards of care**

- **WMA 2000**: uses the terms 'best proven' or 'best current' 'prophylactic, diagnostic, and therapeutic methods' when discussing the nature of treatment that should be provided to trial participants. It is not clearly stated that this standard would be the best proven treatment available anywhere in the world but some have interpreted it accordingly (paragraph 29).
- **CIOMS 2002**: 'For many indications … there is more than one established 'current' intervention and expert clinicians do not agree on which is superior. In other circumstances in which there are several established 'current' interventions, some expert clinicians recognize one as superior to the rest; some commonly prescribe another because the superior intervention may be locally unavailable, for example, or prohibitively expensive or unsuited to the capability of particular patients to adhere to a complex and rigorous regimen. 'Established effective intervention' [refers] to all such interventions, including the best and the various alternatives to the best' (Introduction).
- **NCOB 2002**: 'universal standard of care' is used to 'indicate the best current method of treatment available anywhere in the world for a particular disease or condition. For most diseases and conditions, this standard of care is routinely available to only a small proportion of the world's population' (Box 7.1).

For the purposes of this discussion we will use the term 'universal standard of care' as it is defined by NCOB above; the term 'non-universal standard of care' refers to regional and local standards that might entail a lower level of care.

The standard of care that should be provided to the control group during research

Guidance

3.6 The Declaration of Helsinki (WMA 2000, paragraph 29) is interpreted by some to demand provision of a universal standard of care to a control group, regardless of where the research takes place:

> 'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods.'

3.7 However, CIOMS 2002, CoE 2004 and NCOB 2002 acknowledge that in some circumstances, a non-universal standard of care might be permissible[2] (Appendix A, Table 2). As NCOB 2002 describes:

> 'If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.'[3]

A non-universal standard may be acceptable for trials comparing different standards of care, where the universal standard is not available or feasible, and for investigations of preventive measures. NCOB 2002 specifies that the standard of care must be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees.

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2 CIOMS 2002, Introduction and Commentary on Guideline 11; CoE 2004, Explanatory Report, paragraph 120; NCOB 2002, paragraph 7.29.

3 NCOB 2002, paragraph 7.30.

Workshop discussion

3.8 During discussion, delegates reported that local ethics committees appear to be increasingly sympathetic to the use of regional and local standards as a comparator, rather than a universal standard, for clinical trials. However, decisions about standards of care depended on the context of the research. There was agreement that formulating general advice that could be applied to all situations was difficult (see Box 3.2).

3.9 It was also suggested that even if it was not feasible to provide a universal standard of care in developing countries, researchers should aspire to provide as high a standard of care as possible. From this perspective, the guidance could be interpreted as encouraging researchers to move towards the highest attainable standard of care. However, delegates acknowledged that the costs of providing a particular standard of care may not be confined merely to the cost of providing medicines, but may also include the related costs of improvements to the healthcare system and infrastructure (see also Box 3.5).

3.10 The following points were also made:

- How should the 'best proven therapy' or other standards of care be defined, and by whom?
- The standard of care to be provided should be discussed in the context of the national system for public health.
- Some delegates considered that it would not be appropriate to use a universal standard of care for trials intended to assess the best way for a government health department to provide an intervention for a particular disease. For example, some research might compare the standard of care proposed by the government with the actual standard of care. In such situations, using a universal standard as the comparator would not be relevant.

The use of placebos

Guidance

3.11 The guidance generally agrees that placebo-controlled trials are justified when there is no other proven treatment[4] (Appendix A, Table 2). However, the use of a placebo remains controversial when an effective treatment does exist. In 2002, the WMA published a Note of clarification on the use of placebos stating that, where proven therapy is available, they may be used only 'for compelling and scientifically sound methodological reasons' or when the risks to the participants are insignificant and the condition being studied is minor.[5]

3.12 CIOMS 2002 diverges from the WMA 2000 by concluding that placebos used in place of an 'established intervention' may be ethically acceptable in specific cases. For example, in a country where an established effective intervention is not generally available or affordable, and unlikely to become so in the foreseeable future, research using a placebo may be acceptable in order to develop an affordable intervention specifically for that region.[6] EGE 2003 and NCOB 2002 are in accord with this provision[7] (Appendix A, Table 2). The EGE guidelines specify that the use of placebos in a developing country should be regulated by the same principles that would apply in the EU but use of a non-universal standard may be justifiable:

'An obvious [exception] is when the primary goal of the clinical trial is to try to simplify or

4 WMA 2000, paragraph 29; CIOMS 2002, Guideline 11; CoE 2004, Article 23.3.

5 WMA 2000, Note of clarification on paragraph 29, December 2002.

6 CIOMS 2002, Commentary on Guideline 11.

7 EGE 2003, paragraph 2.10; NCOB 2002, paragraph 7.30.

to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost.'[8]

Workshop discussion

3.13 Some delegates were concerned that controversy over the use of placebos has had a significant impact, not only on research, but also on the wording of national guidance. For example, in Brazil, a placebo may only be used in cases where no proven 'established effective treatment' is available.

Box 3.2: **Interpretation of the guidelines on standard of care – pneumococcal trials**

Pneumococci are bacteria that cause acute respiratory disease, ear infections, meningitis and septicaemia. At least 1 million people a year are estimated to die as a result of infection by these bacteria. The majority of deaths occur in young children and older adults, and the primary cause of death is pneumonia.

Africa bears the greatest burden of childhood pneumococcal disease. The prospect of infant pneumococcal vaccination increased in the 1990s when a large clinical trial was planned to take place in The Gambia. The trial aimed to determine the impact of a pneumococcal vaccine on the frequency of severe infections, and the primary endpoint was to be child survival. The trial was sponsored by NIH under an Investigational New Drug (IND) agreement with the US Food and Drug Administration (FDA), together with the US Agency for International Development (USAID) and the Bill and Melinda Gates Children's Vaccine Program. Ethical review was provided by committees in The Gambia and the UK, as well as the WHO in Geneva. An international Data and Safety Monitoring Board monitored safety data. An individually randomised controlled trial was approved: one group of children would receive the DTP-Hib combination vaccine (for diphtheria, tetanus, pertussis and *Haemophilus influenza* type B) mixed with the pneumococcal vaccine at 6, 10 and 14 weeks of age, while the control group would receive the DTP-Hib vaccine mixed with an inert 'placebo'.

In February 2000, a pneumococcal vaccine was licensed for use in US infants. Bacterial antigens from seven different pneumococcal serotypes were used to produce the 7-valent vaccine. These seven serotypes cover 85% of disease in the US. However, in developing countries two additional serotypes, types 1 and 5, are prevalent. For the trials in The Gambia and South Africa, the company manufacturing the vaccine produced a 9-valent vaccine that included these two additional serotypes.

The trial in The Gambia started in August 2000. After it was well underway, the company decided to cease production of the DTP-Hib combination that was used to dilute the non-licensed 9-valent study vaccine. Existing supplies were sufficient for the enrolment of only half of the original sample of participants. A modified design to maintain the original sample size, was prepared. However, informal dialogue with US government officials indicated that it was likely that the modified trial would not be considered to be in compliance with the 2000 Revision of the Declaration of Helsinki. This was because the design did not allocate the new 7-valent pneumococcal conjugate vaccine which was by then licensed for use in the US, to the control group. Consequently, the modified design was dropped and not formally submitted to FDA.

Continued

8 EGE 2003, paragraph 2.10.

> The original trial design was modified again to account for the limited availability of the DTP-Hib vaccine. The sample size of the trial was reduced which meant that there was insufficient statistical power to make child survival the primary endpoint. It was therefore formally changed to the incidence of radiologically proven pneumonia. The trial with the smaller sample size is now complete, and the results will be reported soon.
>
> A literal interpretation of the Declaration of Helsinki, by officials far removed from the setting in which the trial was being conducted, potentially reduced its value by compromising examination of its initial primary end-point, child survival, which would be of greatest relevance in deciding the future public health value of the vaccine.

3.14 Whether or not the use of a placebo is acceptable will depend on the nature of the disorder and the prevailing health care system. For example, when a treatment for onchocerciasis (river blindness) was being assessed in a clinical trial in the mid-1980s, the use of a placebo could be justified. At the time, two medicines were regularly used to treat onchocerciasis, diethylcarbamazine (DEC) and suramin. As both could cause frequent and often serious side effects, their use was restricted to selected patients. When clinical trials of a new medicine (ivermectin) were planned, a placebo rather than the local 'standard of care' was used because participants receiving either DEC or suramin could have been harmed. This approach was supported by the results from smaller scale pre-clinical trials (Phase I and II) which compared both ivermectin and DEC against a placebo. These demonstrated that ivermectin was as effective, and much safer, than DEC.[9] However, in trials of a treatment for malaria, the use of a placebo is unlikely to be acceptable because the disease could be fatal if left untreated. Delegates agreed that use of placebos would have to be considered on a case by case basis.

3.15 Other situations in which it was suggested that the use of a placebo might be acceptable included:

- the treatment of non-infectious diseases, especially when the disease itself is of a mild and not permanently incapacitating nature, such as headache;
- a treatment being re-tested to account for regional variation in efficacy; and
- the treatment of acute diseases where the standard of care available in developed countries was not easy to attain in the health system settings of developing countries. In addition, where the use of that standard of care would preclude the possibility of detecting effects of interventions that were better than existing therapy but not as effective as the treatment available in developed countries.

The obligations of sponsors

Guidance

3.16 With regard to the provision of care, most of the guidance does not address the obligations of sponsors (Appendix A, Table 2). However, EGE 2003 states that where research participants do not receive a standard treatment of care because of the cost, it must be provided by the sponsor.[10]

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9 For details of formal control trials of ivermectin against DEC see Awadzi K, Dadzie KY, Schulz-Key H *et al*. (1986) The chemotherapy of onchocerciasis. XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in northern Ghana *Ann Trop Med Parasitol* **80**: 433-42; Dadzie KY, Bird AC, Awadzi K *et al*. (1987) Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis *Br J Ophthalmol* **71**: 78–85.

10 EGE 2003, paragraph 2.12.

Workshop discussion

3.17 The requirement that sponsors should meet the costs of a higher standard of care than the best available as part of a national health system may have far reaching implications. There were fears that some funding agencies would be unwilling to support trials in which such costs were substantial. One suggestion was that sponsors should endeavour to ensure that the standard of care provided was aligned with a healthcare practice that was locally sustainable.

3.18 The obligations of sponsors to pay for routine care for all research participants in a trial were also discussed. In South Africa, the MRC Guidelines specify that all participants in trials for HIV-1 vaccines should have access to high quality treatment financed by the sponsors (see Box 3.3). Long-term care of participants who were HIV positive, or who suffered from chronic diseases such as hypertension or diabetes, is also likely to entail significant costs (see Chapter 4). We consider the question of the general provision of care to all trial participants in paragraphs 3.19–3.24.

Box 3.3: **Obligations of sponsors – provision of treatment for HIV-1 vaccine trial participants**

In South Africa, the Guidelines on HIV vaccine research* specify that:

- trial participants should have access to high quality treatment, and
- this access should be financed by trial sponsors.

Thus, participants who become infected with HIV during vaccine trials should be provided with ART when it is medically indicated. Provision could be achieved by means of a national trust fund managed by a healthcare service provider. Participants who become infected during trials could be issued with an identity card and telephone helpline number. This would provide access to a national network of doctors and practitioners for HIV-related treatment and care from anywhere in the country.

Treatment and care, provided via the trust fund, could be financed by sponsor agencies, who would commit a fixed amount of money for each infected volunteer to cover the costs for at least ten years.† Some international agencies have already agreed in principle to the proposed mechanism. However, the approach may not suit low-income countries without an appropriate healthcare infrastructure.

* Medical Research Council of South Africa *Book 5 Guidelines on ethics for medical research: HIV vaccine trials* (SA MRC). These guidelines were compiled by HAVEG (HIV AIDS Vaccines Ethics Group) in collaboration with the Interim National Health Research Ethics Committee (INHREC) and the Medical Research Council of South Africa (MRC).

† Tucker T and Slack C (2003) Not if but how? Caring for HIV-1 vaccine trial participants in South Africa *Lancet* **362:** 995.

The general provision of care to trial participants

Guidance

3.19 Questions about the general provision of care that should be provided to participants who require treatment of conditions that are unrelated to the trial are not addressed specifically in the guidance (Appendix A, Table 2). NCOB 2002 recommends that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Agreement should be reached about what is to be provided before research begins and the proposal should be discussed by the research ethics committee.[11]

11 NCOB 2002, paragraph 7.35.

Workshop discussion

3.20 There was wide support for the general principle that issues relating to standards of care should be discussed before a trial started. Consideration of the level of provision of care was required to allow practical, feasible and innovative solutions to be developed. It was suggested that sponsors should consult closely with local experts and national health authorities (see Box 3.5). However, it was not always clear who should be involved in such discussions, or how they should be initiated.

3.21 When considering the level of care to be provided in any setting, delegates agreed that the implications in the longer term should also be considered, with a view to encouraging and ensuring sustainability (see also paragraphs 6.7–6.8). The provision of treatment or the maintenance of a facility after the research is over (see paragraphs 4.12–4.13) were also raised as longer term, but important, considerations. Two particular situations were identified when discussing the level of care to be provided to all participants: the provision of care for conditions related to the trial and the provision of care for other conditions, unrelated to the trial.

The provision of care for conditions related to the trial

3.22 Delegates acknowledged that the nature of the disease under study was a crucial determinant of the kind of care that should be provided. Different issues were raised by vaccine trials and trials involving chronic diseases, such as hypertension or diabetes. It was also suggested that changing circumstances may influence what is seen to be ethically acceptable. This was illustrated, for example, by the provision of insecticide-treated nets in trials of a malaria vaccine (see Box 3.4) as nets are now increasingly accepted as routine care. Similarly, the provision of anti-retroviral treatments (ARTs) in HIV intervention trials has been particularly problematic (see Box 3.5), but may become less so as the cost of therapy falls and availability in developing countries improves.

Box 3.4: **Provision of care – the changing use of insecticide-treated nets (case study contributed by Professor Brian Greenwood)**

Investigators have found it advantageous to conduct trials of vaccines or preventive medicines for malaria without providing participants with insecticide-treated nets (ITNs), since this allows trials to be smaller and cheaper. Until recently, even if provision of ITNs was part of a national policy for malaria control, it was not being implemented in trials. Ethics committees had accepted that it was unnecessary for sponsors to provide ITNs. However, the national malaria control programmes of many malaria-endemic countries are now making strenuous efforts, by means of donations from the Global Fund and others, to increase coverage of ITNs. Although coverage may still be low, the use of an ITN is becoming the routine standard of care. Ethical opinion is moving towards the view that it should be the responsibility of the sponsors to provide ITNs for all participants in malaria-related medicine or vaccine trials. Once a certain level of ITN coverage is reached, the scientific questions being addressed in trials will focus on the impact of a new intervention when used *in addition* to ITNs.

3.23 One example discussed by delegates concerned a study in Pakistan that investigated the cause of respiratory tract infections in children who lived in a densely-populated slum. The researchers had to consider questions about the level of treatment that should be given to those found to be infected. The nearest public hospitals had very low standards, and lacked both medicines and facilities for adequate care. The University Hospital where the researchers were based had much higher standards. Should infected children be given the

standard of care of the University Hospital or the local standard of care in their community? The researchers decided that most children with mild illness would be given oral antibiotics. Those requiring hospitalisation would be referred to nearby public hospitals or clinics.

3.24 Delegates suggested that, in general, there would be a clear obligation on the researchers to provide care for the condition under study. It was less clear for what length of time care should be provided. In the case of acute disease, the provision of a higher standard of care might be feasible, but treatment of chronic diseases raised particularly difficult questions. Should the obligation last for one year, ten years or a lifetime? Similar questions are posed by the provision of ARTs in HIV intervention trials (see Box 3.5 and Chapter 4).

Box 3.5: **Provision of care – HIV intervention trials (case study contributed by Professor Jimmy Whitworth)**

The provision of ART is increasingly accepted as the appropriate standard of care for people with symptomatic HIV disease. A number of sponsors conducting HIV vaccine trials have agreed to provide ART for trial participants who become HIV positive during the trial.* For example, the International Aids Vaccine Initiative (IAVI), in its Treatment and Care Policy, has made a commitment to support the provision of ART (when clinically indicated) for participants who become infected during an IAVI trial, for up to five years. The HIV Vaccine Trials Network (HVTN), sponsored by the National Institutes of Health Grants (NIHG) and National Institute of Allergy and Infectious Diseases (NIAID), has developed a strategy for a fund to pay for treatment, and the South Africa Aids Vaccine Initiative (SAAVI) has proposed an insurance scheme (see also Box 3.3). However, it is unclear how these proposals will work in practice, and the approach raises a number of issues:

- Supplying ARTs requires greater commitment than merely purchasing of the medicine. Where there is currently no ART provision in place, it will also be necessary to provide additional infrastructure and improvements in healthcare facilities.
- When a low-technology, low-cost intervention for HIV is evaluated, such as the use of a microbicide or a behavioural intervention, the costs of ART provision would be significantly higher than the costs for the intervention itself. If the provision of ART is required as part of the trial, the cost may be regarded as prohibitive by the sponsors.
- What standard of care should be provided for those who develop HIV during the course of the study? These individuals are not likely to begin to require ART until five years or more after infection, by which time the study is likely to have been completed. Should ART be provided after the end of the study? How can this be arranged?
- What treatment should be provided for individuals found to be already HIV positive when they are screened for entry into a trial? Although they will not be eligible to participate, significant numbers are likely to require ART immediately (as they may have had HIV for some time), potentially increasing the costs of the trial.

It was suggested that researchers should work with local authorities to facilitate the provision of ART. This would encourage a longer term improvement in the provision of healthcare in the region and allow a sustainable approach. It would also reduce concerns about patients being coerced to take part in a trial, because they would be more likely to receive ART locally, regardless of whether they participated.

* Fitzgerald DW, Pape JW, Wasserheit JN *et al*. (2003) Provision of treatment in HIV-1 vaccine trials in developing countries *Lancet* **362**: 993–4; Berkley S (2003) Thorny issues in the ethics of AIDS vaccine trials *Lancet* **362**: 992.

The provision of care for other conditions

3.25 Where a condition unrelated to that directly under study was present in a participant, delegates agreed that a suitable referral to the local health services may be appropriate. However, the mechanism for such a referral would need to be considered in advance and agreed with the local health authorities before the research begins. Particular difficulties may arise if the facilities for appropriate care were not available locally.

3.26 An unrelated condition might also be discovered indirectly and not as a direct consequence of research during the course of a trial. It was suggested that in this situation, there may be a lesser obligation on a researcher regarding the provision of care, but a suitable referral should be made. An example was given of a female sex worker in Benin, who was found to have pelvic inflammatory syndrome (resulting from an extra-uterine pregnancy) during a trial of a vaginal microbicide. The patient was referred to a gynaecology clinic, which asked for advance payment before performing an operation. Although this type of situation had not been envisaged when the study was planned, the sponsors agreed to pay the fee for the operation. It was suggested that in situations where the healthcare infrastructure was poor, research teams may be obliged to provide some level of care for all conditions. However, delegates agreed that the extent of this commitment should be assessed on a case by case basis and the approach adopted should be subject to approval from an ethics committee.

Summary of discussion on standards of care

3.27 It was clear during discussion at the Workshop that the nature of treatment that should be provided to participants during research remains a particularly controversial issue. Concerns were expressed that, by aiming only for the very best treatment, or a universal standard of care, potentially beneficial research may be prevented.

3.28 Several themes emerged throughout the Workshop. These were:

- The use of a regional or local standard of care as a comparator is now seen to be acceptable in some situations, as set out in the guidance of CIOMS 2002, CoE 2004 and NCOB 2002.
- It is unhelpful to generalise about the standard of care that should be provided, both to the control group and to all participants. Reaching an answer that can be applied in all situations is difficult, but a careful case by case assessment, which acknowledges the limitations of local and regional practicalities, may be useful.
- Discussion between relevant stakeholders should begin at the planning stage of any trial. Researchers, sponsors, local and national health authorities should work together to ensure acceptable solutions are developed.
- Controversy over placebos has led to unrealistic requirements in the guidance that might discourage valuable research.
- Requiring sponsors to meet costs of a universal standard of care may have far reaching implications, some of which may be detrimental to public health.
- Particular difficulties arise when provision of general care to all participants is contemplated. These issues are not addressed in the guidance.
- Issues of longer term sustainability should also be considered (see also paragraphs 6.7–6.8). Researchers should try to ensure that improvements in healthcare offered during research are achieved in such a way that the benefits are sustainable after the work is complete.

Chapter 4

What happens once research is over?

What happens once research is over?

Introduction

4.1 Externally sponsored research in developing countries raises ethical issues not only during research but also once the clinical trial or study is over. Researchers, sponsors and research ethics committees have to consider whether an intervention found to be efficacious in a completed trial should continue to be provided to the research participants, and to the local community. Many people would like to see participants given guaranteed access to interventions shown to be successful once the research is complete. However, subsequent access to successful interventions or the maintenance of an improved standard of healthcare to participants, and especially to the wider community, is rarely a simple matter. Providing access will depend upon several factors including the existence of alternatives, the relative burden of the disease, and the costs of supplying treatment. Expensive interventions that initially appear too costly to implement may become affordable within a short period of time.

4.2 Uncertainty about whether an experimental intervention will prove to be successful or locally affordable, and the difficulty of guaranteeing that it can be provided to participants in the longer term, have discouraged sponsors from making commitments of this nature before embarking on a trial. The possibility of introducing an intervention may depend on support from external bodies, other than those sponsoring the research, as well as action by national governments. How much effort should be made by sponsors to secure access in order to ensure that research is ethically acceptable is therefore difficult to judge. There is a growing consensus however, that the ethical review process, undertaken before the research starts, should address the issues that may arise when the trial or study is concluded. (See also NCOB 2002, Chapter 9.)

4.3 In the Workshop, three issues that arise once research is complete were considered:

- should post-trial treatment be provided?
- who should supply treatment or provide interventions?
- determining when research is over.

Should post-trial treatment be provided?

Guidance

4.4 In general, there is consensus in the guidance that participants should benefit from taking part in research [1] (Appendix A, Table 3). For example, WMA 2000 requires that:

> 'At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.' [2]

However, recent discussion at the WMA about a proposed revision to this paragraph led to 'sharp differences of opinion'. It was eventually agreed that the paragraph should not be amended but that a Note of clarification should be added (see Box 4.1).

4.5 WMA 2000 does not define in any detail how the requirement to assure access to treatment should be achieved. EGE 2003, however, specifies that 'free supply of a proven beneficial new drug' must be arranged for all the participants of a trial after the trial is ended, provided that

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1 WMA 2000, paragraph 30; CIOMS 2002, Guideline 10; EGE 2003, paragraph 2.13; NCOB 2002, paragraph 9.31; National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 4.1.

2 WMA 2000, paragraph 30.

the intervention is not available 'through the normal health care system', and that this may involve 'supplying the drug for a lifetime if necessary'.[3] EGE 2003 also states that the clinical trial should benefit the community that contributed to the development of the drug. This could be achieved by guaranteeing a supply of the drug at an affordable price for the community, or by strengthening expertise.

4.6 NCOB 2002 and CIOMS 2002 acknowledge that it may not be possible in all cases to ensure post-trial access. However, they recommend that possible options should be clarified before the trial begins.[4] CIOMS 2002 notes in Guideline 10 that:

> 'Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that … any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.'

The Commentary on Guideline 10 notes that 'for minor research studies and when the outcome is scientific knowledge rather than a commercial product, such complex planning or negotiation is rarely, if ever, needed.'

Workshop discussion

4.7 The main doubt expressed by delegates was that it was unlikely to be feasible for sponsors to guarantee provision of an effective intervention after a trial in all circumstances. This was particularly true if continued treatment for chronic disease was involved as costs could be high in the long term.

4.8 There was support for the principle of addressing questions concerning availability of treatment at the planning stage. Delegates acknowledged that this approach may be difficult because the price of a medicine cannot be predicted before a trial is completed. However, considering the issues before the trial starts is likely to be beneficial; negotiations during the study or after its completion could lead to undesirable tensions and delays in making interventions available. Some delegates were concerned that an unrealistic burden would be placed on researchers if they were expected to secure post-trial access for participants. Others cited instances where such advance negotiation had been successful. For example, during trials of ARTs in Uganda and Zimbabwe, the sponsors and pharmaceutical companies had made it clear they would not pay for ART once the trial was over. However, the local ethics committees took the view that the trial was, on balance, beneficial to participants, in part because they would receive ART for four years. The researchers had then been able to obtain written confirmation from the relevant Ministers of Health accepting responsibility for continuing care of trial participants, including the continuing provision of ART. It was agreed that it would have been unrealistic to expect more than a provisional guarantee for lifelong therapy.

4.9 It was suggested that options for the availability of post-trial treatment for the wider community should also be explored. The main purpose of conducting clinical trials was to evaluate interventions that may have application in populations, of which the participants in the trial were but a sample. However, the guidance offers little advice about wider provision, which would be especially relevant to vaccine trials. A number of questions need to be considered. If a vaccine was found to be effective, who should provide it to the community? How many people should be treated? For how long should the vaccine be supplied? What additional costs would be involved? And most importantly, who should be responsible for

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3 EGE 2003, paragraph 2.13.

4 CIOMS 2002, Commentary on Guideline 10; NCOB 2002, paragraph 9.31.

meeting those costs? Delegates agreed that these questions should be addressed in advance.

4.10 However, delegates also noted that in making the intervention available to all participants in a study or the wider community, the possibility of long-term surveillance to assess the safety of a treatment may be excluded. There would no longer be a control group for comparison with participants who received the intervention, which may make it difficult to detect later adverse effects. NCOB 2002 observes that this issue is not confined to clinical trials in developing countries and recommends that judgements would have to be made on a case by case basis.[5]

Box 4.1: **Revision of WMA Declaration of Helsinki paragraph 30**

Paragraph 30 of WMA 2000 concerning the provision of treatment to research participants reads:

> '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.'

The WMA established a Workgroup to consider an amendment to paragraph 30 of WMA 2000 in October 2001. However, 'sharp differences of opinion' at the WMA General Assembly in September 2003, led to the amendment not being adopted.* Instead, another Workgroup was established to clarify the controversy. The Workgroup's Report outlined three options:

- not to revise paragraph 30, but to add preamble explaining that the Declaration is not a regulatory or legal device;
- to add a note of clarification setting out the intention of the paragraph; or
- not to make any changes and to issue a separate statement on equitable access to healthcare.†

The proposed revisions to paragraph 30 were discussed during the Workshop. The Council submitted a response to the Workgroup's Report which drew on this discussion and the Council's 2002 (NCOB 2002) Report.‡

In May 2004, the Workgroup announced its decision that paragraph 30 would not be amended and nor would a preamble be added. However, a Note of clarification was later added to the Declaration stating that:

> 'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.'∫

* World Medical Association (2003) Press release 14 Sept *WMA to continue discussion on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2003_19.htm Accessed on 3 Feb 2005.

† World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki*.

‡ Submission by the Nuffield Council on Bioethics to WMA. Available: www.nuffieldbioethics.org/developingcountries Accessed on: 3 Feb 2005.

∫ World Medical Association (2004) Press release 11 Oct *Clarification on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2004_24.htm Accessed on: 3 Feb 2005.

5 NCOB 2002, paragraphs 9.17–9.20.

Who should supply treatment or provide interventions?

Guidance

4.11 Most of the guidance does not address the question of where the responsibility of providing interventions after research is over should lie (Appendix A, Table 3). Neither WMA 2000 nor EGE 2003 comments on which organisation should supply treatment. However, CIOMS 2002 states that it is the sponsor who should provide post-trial access to treatment.[6] In contrast, NCOB 2002 concluded that the provision of new medicines or improved healthcare was primarily the responsibility of national governments, and that sponsors of research were not in a position to make unilateral decisions at the start of a trial without appropriate consultation.[7]

Workshop discussion

4.12 Delegates acknowledged that decisions about post-trial treatment involved several different stakeholders, and that it was important to recognise the complex interplay between them. They included sponsors (both public and private), local governments, policy makers, researchers and physicians. There was some debate as to whether it was either useful or realistic to consider these stakeholders as members of a 'team' but it was suggested that, in any event, it was important to establish an early dialogue between these different groups (see Box 4.2). It was suggested that continued discussion might help to establish a transparent and efficient mechanism for providing post-trial treatment, and by defining shared responsibilities, it would be possible to ensure sustainability and independence.

Box 4.2: **Providing the intervention after the trial is over – ARTs in Brazil (case study contributed by Professor Carlos Brites)**

In Brazil, a Resolution advises that 'Access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter, if there is no sponsor, in the event its superiority to the conventional treatment is proven'.*

Researchers designing a trial for ARTs to treat HIV/AIDS patients, initially faced resistance to this requirement, because of the high price of the medicines. However, after negotiation, all companies involved in sponsoring the trial agreed to comply. In one particular trial investigating the medicine Enfuvirtide (T-20), a pharmaceutical company provided supplies for more than two years after the trial was completed, without cost to the participants. The Brazilian Ministry of Health is currently negotiating with the company to buy T-20 for the public health system. It is expected that patients will continue to receive the medicine in the same way but the provider will be the government rather than the company.

* Resolution 251 (251/97/IV.1.m) Brazilian National Health Council.

4.13 The roles of particular stakeholders that were discussed included:

- *Sponsors:*

  Delegates recognised that if researchers or sponsors were categorically required to fund the future provision of interventions, either to participants in the study or to the wider community, many would be likely to cease supporting research. In particular, sponsors from the public sector are unlikely to be able to bear the costs involved without curtailing other research.

6 CIOMS 2002, Guideline 10.

7 NCOB 2002, paragraph 9.36.

- *Physicians:*

One of the suggested revisions for paragraph 30 of WMA 2000, which was under consideration at the time of the Workshop by a WMA sub-committee (see Box 4.1), stated that physicians 'should make every effort to ensure that all patients… will have access to any … therapeutic method'.[8] However, delegates observed that this wording was problematic. Although the primary support should come from physicians, they would seldom be in a position to guarantee availability of treatment. The role of other stakeholders needed to be acknowledged. In addition, it may be more realistic to suggest that those involved should make 'appropriate efforts' rather than 'every effort'.

- *National government:*

It was suggested that it was important to assess the capacity of national health care systems to introduce and sustain interventions. Research should be aligned with, and aim to strengthen, existing national health programmes. Researchers and sponsors should be proactive in liaising with relevant government departments to ensure the availability of treatment after a trial. Involving the community at an early stage should also help to develop long-term solutions that are feasible and realistic so that services can be maintained after the study is completed (see also Box 3.5). It was observed that further analysis, and consideration of other factors such as national priorities, cost-effectiveness and other research findings, would often be necessary to determine whether an intervention should be implemented. Such evaluation should be the responsibility of policy makers.

When is research over?

Guidance

4.14 The question of how to determine when a study, trial or research project is complete is not addressed in the guidance. However, delegates considered a proposed revision of paragraph 30 of WMA 2000, which, had it been approved by the WMA General Assembly, would have required a new intervention to be made available 'once it has been approved by the appropriate authorities'.[9]

Workshop discussion

4.15 Delegates agreed that it is not always a straightforward matter to determine when research is complete. Not all research leads directly to useful interventions that can be introduced into routine care. The requirement that treatment should be made available after all clinical trials is, therefore, not meaningful, and delegates suggested that the issue should be clarified in the guidance. Examples of research that would not necessarily result in a treatment being made available included:

- Phase I trials that do not immediately result in proven treatment (see Box 4.3).
- Single research studies: these rarely lead to the discovery of a new intervention that can be introduced immediately into routine care. Operational research to define how a new intervention may be integrated into the healthcare system and the feasibility of its introduction need to be addressed before access can be agreed.

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8 World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.1. and 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005.

9 World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005. See also World Medical Association (2004) Press release 11 Oct *Clarification on Declaration of Helsinki*. Available: http://www.wma.net/e/press/2004_24.htm Accessed on: 3 Feb 2005.

- Epidemiological and observational studies, which do not usually translate into new medical interventions.[10]

Box 4.3: **No immediate implementation of treatment – clinical trials of antimalarial treatments (case study contributed by Professor Malcolm Molyneux)**

A research project was conducted in Blantyre, Malawi, to determine whether artesunate suppositories could provide initial beneficial therapy for children with severe malaria (see Box 2.2). A number of practical issues arose during discussion about the availability of treatment after the completion of the trial. It would not be possible to implement the treatment immediately and, in addition, it was not envisaged that the intervention would be provided to the trial participants themselves because:

- The trial participants were not the eventual target group of the research. The trial involved children with 'moderately severe' malaria, whereas the final therapy was intended for children with severe life-threatening malaria.
- The project involved an immediate short-term treatment for an acute disease. Participants in the trial would not require continuous therapy, although they may experience possible future episodes of the disease.
- The trial was an early efficacy study. Introduction of the treatment would require subsequent effectiveness studies. It would also be necessary to establish additional facilities to deliver the intervention before it could be made widely available.

See Barnes KI, Mwenechanya J, Tembo M, McIlleron H, Folb PI, Ribeiro I, Little F, Gomes M, Molyneux ME (2004) Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study *Lancet* **363**:1598-605.

4.16 Researchers, sponsors and local health authorities may differ in their view of how successful a trial has been. Questions were raised about how effective an intervention must be shown to be before it merits provision. For example, if a vaccine is shown to give a 50% protection, should it be widely introduced?

4.17 Delegates noted that guidelines requiring a new intervention to be made available 'once it has been approved by the appropriate authorities'[11] may not always be practical for two reasons:

- There may be a risk that suspending the provision of treatment until regulatory approval will leave trial participants without treatment. This would be especially relevant in the case of trials of interventions to control potentially fatal chronic conditions.
- It could also lead to delay in the provision of treatment to the wider community. If trials of interventions are sufficiently advanced, the question of access could be explored before full regulatory approval. This is especially important in the case of interventions regarding life-threatening or seriously debilitating conditions where alternative interventions are ineffective or unavailable.

Summary of discussion about what happens once research is over

4.18 Wherever possible, the results of trials where interventions prove to be effective must be translated to improve healthcare for communities in which they were undertaken. It was

10 See also NCOB 2002, paragraph 9.34.

11 Under consideration at the time of the Workshop by a WMA sub-committee established to review paragraph 30 of WMA 2000, see World Medical Association (2003) Workgroup Report on the revision of paragraph 30 of the declaration of Helsinki, paragraph 3.2. Available: http://www.wma.net/e/pdf/wg_doh_sept2003.pdf Accessed on: 3 Feb 2005. See also Box 4.1.

agreed, therefore, that discussions about what should happen once research is over are particularly crucial. However, most of the guidance does not address the practicalities of the provision of interventions, or where the responsibility should lie.

4.19 Several themes emerged throughout the Workshop. These were:

- It is essential to begin negotiations about post-trial treatment at an early stage when planning research. This reaffirms the recommendations of CIOMS 2002 and NCOB 2002, and the recent Note of clarification added to WMA 2000, which states that it is necessary to identify post-trial access 'during the study planning process'.
- Early discussions should be held between a range of different stakeholders, including sponsors, researchers and physicians, health authorities and governments. However, there is no agreed mechanism for such negotiations.
- Governments need to assess the capacity of national health programmes and consider issues of the consequences of providing new interventions when allocating resources. For example, if a hepatitis B vaccine were introduced into an infant vaccination programme, would this prevent the provision of other interventions as a result of limited resources?
- It is unlikely to be feasible in practice to guarantee provision of an effective intervention after a trial in all circumstances. Guidance that requires researchers or sponsors to fund the provision of interventions once the research is complete may be unrealistic and lead to sponsors curtailing other research.
- It is not always a straightforward matter to determine when research is complete, and some of the requirements in the guidance to provide post-trial access might not always be feasible.
- Research has the potential to provide benefits to a community that are not confined to the provisions of the particular study and these may be more enduring than the provision of the tested intervention. These benefits may include:
  - increasing the number of people able to contribute professionally to healthcare;
  - assisting the development of the skills and expertise of local scientists;
  - improving health infrastructure; and
  - increasing the potential for a sustained improvement in healthcare services (see also paragraphs 6.7–6.8).
- Attention should be given to these potential improvements during discussion about the post-trial availability of treatment to both research participants and the wider community.

Chapter 5

Ethical review

Ethical review

Introduction

5.1 An effective system for ethical review of research provides a crucial safeguard for research participants. While this process is typically undertaken by independent Research Ethics Committees (RECs), there are still many countries in the developing world in which these bodies are absent, ineffective or under-resourced. In addition, there may not be a pool of sufficiently trained and independent people to serve on such committees. As we have said, the inequalities in resources that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out. The structure of RECs, the scope of their work and the mode of their operations are therefore particularly important in the context of research in developing countries.

5.2 A critical issue is whether there should be separate scientific and ethical review, and whether review should take place in both the sponsor's country and the country in which research is to be conducted (the host country). The independence of RECs is crucial and their sources of funding need thorough consideration. The scope of the responsibilities of RECs also needs to be carefully defined, including their role after a trial has begun, addressing conflicts when more than one ethics committee is involved, and ensuring adequate training for committee members in order to build capacity, skills and experience (see also NCOB, Chapter 8).

5.3 In the Workshop, the following issues were discussed:

- should there be separate scientific and ethical review of research?
- where should review take place?
- what kind of funding and support is appropriate for a REC in the host country? and
- what is the role of a REC after the approval of research?

Should there be separate scientific and ethical review of research?

Guidance

5.4 The guidance generally agrees that ethical review of research should take place and that it should be conducted by at least one independent REC[1] (Appendix A, Table 4). However there are different views regarding the need for separate scientific and ethical review, and whether or not it is appropriate for a REC to review the scientific validity of a study.

5.5 NCOB 2002 recommends that scientific and ethical review should, where possible, be undertaken separately because they have different purposes. This may, but will not necessarily, require the establishment of two committees.[2] In contrast, WMA 2000, CIOMS 2002 and EGE 2003 do not require a separate committee for scientific review.[3] CoE 2004 requires independent examination of the scientific merit of a proposal, followed by ethical review and approval by a 'competent body'.[4]

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1 WMA 2000, paragraph 13; CIOMS 2002, Guidelines 2 and 3; CoE 2004, Articles 9 and 10; EU 2001, Articles 3, 6 and 9; EGE 2003, paragraph 2.8; NCOB 2002, paragraph 8.2.

2 NCOB 2002, paragraphs 8.4 and 8.5.

3 WMA 2000, paragraph 13; CIOMS 2002, Commentary on Guidelines 2 and 3; and EGE 2003, paragraph 2.8. All agree that ethical and scientific review must take place.

4 CoE 2004, Article 7 states: 'Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.' The phrase 'competent body' is used to indicate that in some countries the ethics committee may be the competent body, whereas in others the competent body might be a Ministry or a regulatory agency that would take the opinion of the ethics committee into account, see Explanatory Report, paragraph 28. See also Article 9: *Independent examination by an ethics committee*.

Workshop discussion

5.6 During discussion, there was broad agreement that both the scientific quality, and the ethical issues raised by the proposed research should be reviewed but there was disagreement as to how this should be achieved. Ideally, and where feasible, it was suggested that these review processes should be separated (see also Box 5.1). In Kenya, for example, a scientific committee usually reviews the scientific protocol before it is submitted to an ethics committee. If the scientific committee does not have enough expertise, an external Kenyan expert is sought to review the protocol. In a much smaller country such as Fiji, there are not currently enough suitably qualified experts to make it possible to create two separate committees. One suggestion was that it might be more appropriate to specify that a REC has a duty to ensure that there is adequate review of both the ethical and the scientific aspects of a proposal, rather than stating how this should be achieved.

Box 5.1: **Ethical review in a host country – South Africa (case study contributed by Professor Ames Dhai)**

In South Africa, the National Health Act No. 61 (2003) makes it a legal requirement that any research related to healthcare must have approval from a REC registered with the National Health Research Ethics Council. The Council, appointed by the Minister, is responsible for registering and auditing RECs.

There are currently more than 20 RECs in the country, including Provincial Research and Ethics Committees, RECs in tertiary institutions and private RECs. The Department of Health's Clinical Trials Guidelines (2000) recommend that a REC should include members who have the qualifications and experience to review and evaluate the scientific, clinical, and ethical aspects of the proposed trial.* Most RECs in the country are, therefore, able to conduct both scientific and ethical review, although the processes are often separated. They include:

- Institutional RECs (for example, eight are attached to medical schools): scientists on the committee who have appropriate expertise review the scientific aspects as part of the appraisal of the ethical issues. A separate scientific committee in the institution will also conduct an independent scientific review of undergraduate and postgraduate research projects. The same members may serve on both committees.
- MRC of South Africa Ethics Committee: a scientific review must have been conducted before a project is submitted to the Committee. However, there is also scientific expertise on the Ethics Committee itself.
- Committees of pharmaceutical companies: a pharmaceutical company will usually have an internal scientific committee to review a proposal when sponsoring clinical trials. The local REC will also examine both the scientific and ethical aspects of the proposal.

* South Africa Department of Health (2000) *Guidelines for good practice in the conduct of clinical trials in human participants in South Africa*, Guideline 8.2. Available: http://www.doh.gov.za/docs/policy/trials/trials-full.html Accessed on: 4 Feb 2005.

5.7 Delegates also discussed the development of regional committees for scientific and ethical review. A number of independently established regional fora for RECs have been established such as the Pan-African Bioethics Initiative (PABIN) under the auspices of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). These committees assist with the development of expertise for ethical review, facilitate education and provide technical support. It was suggested that they might also have a useful role where a particularly difficult case is being reviewed, or one that raises new issues. However, such committees need direct

funding for their establishment and continued maintenance, and may not be able to expand their roles accordingly.

Where should review take place?

Guidance

5.8 One of the main points of disagreement in the guidance concerns the degree of involvement of the host country in the review process (Appendix A, Table 4). Three documents recommend that ethical review is undertaken in the host country. For example, CoE 2004 requires that an ethical review by an independent ethics committee be performed 'in each State in which any research activity is to take place'.[5] NCOB 2002 recommends that research should be reviewed in both the sponsoring country(ies) and the host country(ies) in which research takes place.[6] EU 2001 states that an opinion on the ethics of the proposed research should be given by each Member State participating in the trial.[7]

5.9 Other guidelines are less stringent. CIOMS 2002 does not necessarily require host countries to have a distinct fully functioning REC, although representatives from the host countries should be involved in the ethical review process.[8] Similarly, EGE 2003 allows the review to be conducted by a mixed committee, with representatives from both EU Member States and host countries.[9] WMA 2000 is the only guidance that does not address the need to have a REC in the host country.

Workshop discussion

5.10 During discussion, it was observed that proposals for externally sponsored research often have to be submitted to multiple reviews in both the host and sponsor country. A proposal may be reviewed by the REC at the local institution, the REC of the host country, the RECs of collaborators in the sponsor country, internal committees of the sponsors, and by any institutions where laboratory samples are analysed. Concerns were expressed that multiple review can cause long delays and a number of examples were cited. For example, for a study in Malawi, it took one and a half years for a protocol for a vaccine trial to be reviewed. Similarly, in a partnership to conduct a clinical trial of a rotavirus vaccine in India, it took nine months for a protocol to be reviewed by four different RECs. Each REC has a different schedule of meetings. Passing a proposal sequentially between the four committees can take several months. If one REC makes alterations to a proposal, the others will often want sight of the revised version, causing further delays. However, if researchers send their proposal to several committees simultaneously, and the different committees request different revisions, re-circulation of the new draft between all parties can also cause delays (see also Box 5.2).

5.11 If the review process is to achieve its aim of improving the quality of research, the process needs to be made more efficient. One possibility, discussed during the Breakout Groups, would be to improve mechanisms for communication between different RECs reviewing the same protocol. Methods discussed included: encouraging the exchange of information between committees; copying all correspondence to the other RECs as well as to the investigator; and facilitating visits between committees of the host and sponsor countries.

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5 CoE 2004, Article 9. Article 29 also considers the possibility that research might take place in a country that is not party to this Protocol, or in a country where no suitable body for the review of research exists, see Appendix A, Table 4.

6 NCOB 2002, paragraph 8.22.

7 EU 2001, Articles 3.2a and 9.

8 CIOMS 2002, Commentary on Guideline 3.

9 EGE 2003, paragraph 2.8.

Improving the channels of communication would help reduce tensions and conflicts between committees, develop consistency of decisions and also enable better understanding about the local context in which the research is to take place.

5.12 It was suggested that in some circumstances, the responsibilities between committees could be devolved, with individual RECs reviewing only parts of a proposal. This idea accords with CIOMS 2002. These guidelines suggest that RECs in the sponsor country have a specific responsibility to review the scientific methods, whereas committees in the host country should determine whether the objectives of the research are responsive to the health needs of that country, review the detailed plans for compliance, and assess the ethical acceptability of the research proposal in light of the local community's customs and traditions.[10] (See also paragraph 6.23 for further discussion of the role of a REC in assessing the research priorities of a country.)

5.13 For some issues, it was considered essential to include local expertise in the review process. The host REC, with knowledge of the local and cultural context, may be better placed to comment on issues concerning research priorities, consent, inducements and the protection of research participants. However, as discussed earlier (see paragraphs 2.14–2.16 on consent), innovative methods may be required to ensure adequate lay representation (see also Box 6.1). Many RECs already included lay members, but the importance of ensuring that they could contribute effectively needed to be emphasised.

5.14 Another issue concerned the primacy of the host and sponsor committees. In general, it was considered more important to have dialogue rather than dominance between different committees, although there was a need to recognise that committees may differ in their expertise. However, delegates suggested that in most situations the local host committee should be able to make the final decision. In practice, however, it was considered unlikely that a sponsor would be willing to fund a project where either the host REC or the sponsor country's REC had not given approval. Some sponsors require a proposal to have received local REC approval before it is submitted for funding. Such a requirement may prove burdensome for a local committee. If a grant is then not approved, an already under-resourced REC will have wasted both time and effort.

5.15 Some delegates suggested that a substantial expansion in the number of externally sponsored clinical trials in developing countries was likely to occur over the next decade. Greater investment in research by private foundations, and the pharmaceutical industry, and new initiatives such as the European and Developing Countries Clinical Trials Partnership (EDCTP) could be expected to increase pressure on local ethics committees. Under these circumstances, more effective committees that can function well at the local level would be essential.

10 CIOMS 2002, Commentary on Guideline 3.

Box 5.2: **Ethical review in a host country – Brazil (case study contributed by Professor Carlos Brites)**

The National Ethics of Research Committee (CONEP) was established by the Brazilian National Health Council (CNS) in 1996 (Resolution 196/96). CONEP is responsible for the evaluation of all research involving humans, particularly projects involving genetics, human reproduction, indigenous populations, biosafety issues, research supported by foreign countries or institutions, or involving the export of biological materials. CONEP reviews projects after approval has been given by the local REC. It also has a regulatory and advisory role, and manages disagreements between local RECs and researchers.

After a period of adaptation, the system is now considered to be operating well and conflicts between CONEP and investigators are rare. However, there are still concerns about the time taken to resolve issues raised by specific projects. Because a project must be approved at two different levels, it usually takes three to four months for final approval to be received.

What kind of funding and support is appropriate for a REC in the host country?

Guidance

5.16 The guidance agrees that ethical review of research should be conducted by a REC independent of undue financial or political influence[11] (Appendix A, Table 4). However, there is conflicting advice as to the type of support or funding that may be appropriate to enable a REC to function effectively. EGE 2003 states that EU Member States may provide funds directly for capacity building and maintenance of RECs in host countries. CIOMS 2002 considers that sponsoring countries have a responsibility to support the development of capacity of RECs in developing countries, but does not state whether this contribution should be provided to the host country directly or indirectly.[12] In contrast, NCOB 2002 suggests that it is the responsibility of national governments to ensure the functioning of a REC, and recommends that committees should be funded indirectly to prevent problems of bias.

Workshop discussion

5.17 A number of delegates described difficulties faced by RECs in their own countries (see Box 5.3). The situations described reflected problems experienced in several countries, including for example, Peru. It was suggested that direct financial support by the sponsor to the REC may not be the best solution. Instead, funds could be put into a central pool for allocation to individual RECs. However, there were concerns that some institutions did not honour their commitment to support RECs. In the case of collaborative research, for example, a substantial proportion of the funding that was sometimes allocated to the institution for indirect costs often failed to be translated into funding for REC activities.

5.18 A number of different ways in which sponsors could assist the development of RECs in host countries were considered. These included the provision of training, general resources such

11 WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; CoE 2004, Article 10; EU 2001, Article 9; EGE 2003, paragraph 2.9; NCOB 2002, paragraph 8.20.

12 CIOMS 2002, Commentary on Guideline 20: 'External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research.' However, Guideline 2 states that: 'sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol.' This suggests direct funding may be acceptable. NBAC guidelines also agree that 'US sponsors and researchers should assist in building capacity of ethics review committees in developing countries'. See National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 5.7.

as IT and communications equipment, and providing a direct fee for specific services. It was noted that if a committee introduced a charge for reviewing a project to cover the costs, the charge should apply regardless of whether or not the project was approved. In some countries, the fee had sometimes only been charged if a project was approved.

5.19 The importance of providing training for members of RECs was also emphasised. Sponsors could contribute by providing training to members of committees to enhance the skills and understanding of the ethical review process. Initiatives to develop capacity for ethical review were seen to be particularly valuable and sponsors could play an important role in encouraging such programmes. For example, the Wellcome Trust sponsors training opportunities for members of ethics committees in developing countries through its Biomedical Ethics Programme.[13] Delegates pointed out that an adequate infrastructure was crucial to ensure that knowledge acquired could be put into practice.

Box 5.3: **Difficulties faced by local RECs – Kenya (case study contributed by Dr Job Bwayo)**

In Kenya, members of the REC are expected to offer their services voluntarily, although a small amount of money may be available to compensate for time and travel expenses. Almost all of the members have been trained according to good clinical practice guidelines issued by ICH (see paragraph 1.12). They also receive annual training funded by foreign sponsors. However, the rapid turnover of trained staff makes it very difficult to sustain continuity.

Most members are not directly involved in research and find the review of large numbers of research protocols burdensome. The REC has limited office space in a hospital and a university, with no facilities for communication, photocopying or for keeping records. Although there are computers, there is no Internet connection and no access to a resource centre. This makes it difficult for members to perform literature searches or to familiarise themselves with specialised subjects under review.

An independent office for the REC with adequate administrative support is needed. However, this development would require significant additional funding. A small fee is charged for review of protocols but the funds received are retained by the institution and not used to support the REC. Current funding from the government, which is given to the institution rather than direct to the REC, is not adequate to sustain an independent REC.

5.20 Another means of providing additional funding for RECs could be for committees to charge for some of the functions that they perform, such as assessing research proposals at an early stage. It was also suggested that institutions could impose a charge for reviewing grant proposals to provide a source of internal funding to support the administration, and infrastructure required by a REC. However, care would need to be taken to avoid possible conflicts of interest.

5.21 A number of delegates asked about the availability of advice to guide those concerned with establishing RECs. It was noted that the WHO had produced guidelines giving general

13 The Wellcome Trust Ethics of Biomedical Research in Developing Countries grant schemes. Available: http://www.wellcome.ac.uk/funding/medicalhumanities/biomedicalethics. Other examples include initiatives funded by the Fogarty International Center (International Bioethics Education and Career Development Award, see http://www.fic.nih.gov/programs/bioethics/bioethicsaward.html); Harvard University (International Fellowship in Health Research Ethics, see http://www.hsph.harvard.edu/bioethics) and International Research Ethics Network for Southern Africa (IRENSA) (see http://www.irensa.org) (Accessed on: 4 Feb 2005).

standards of practice, including operating procedures and recruitment of members.[14] This advice could provide a sound basis for initiating discussion and could be adapted to fit local circumstances. PABIN, SIDCER and the Council of Europe had also published some relevant literature (see Appendix D).

What is the role of a REC after the approval of research?

Guidance

5.22 Some elements of the guidance (WMA 2000, CIOMS 2002, EU 2001) suggest that RECs have an obligation to follow up research or to conduct monitoring.[15] CIOMS 2002 for example states that:

> 'The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.' [16]

Workshop discussion

5.23 There were some concerns that requiring a REC to monitor a research study after it had begun would increase the already burdensome workload of RECs. In most cases additional resources for monitoring would not be available. Some RECs might be able to achieve passive monitoring. At the very least, where ethical approval was time-limited, a REC might ask for a report before granting renewed approval. In the Caribbean and Pakistan, for example, some RECs give approval for a project to be conducted for one year. The researcher is then asked to provide an annual report on the conduct of the study and to confirm that the protocol is unchanged in order for the approval to be renewed. However, the process had proved to be inefficient because of incomplete reporting and follow-up of non-responders. Furthermore, in many countries, reports from researchers are received by data and safety monitoring boards, which lack a clear mechanism for communication with RECs.

5.24 Several delegates commented that RECs were not always seen to be consistent in their decisions. In some cases, there was anecdotal evidence of researchers 'shopping around' until they found a committee that gave a favourable decision on a project. This practice raised questions about how RECs themselves were reviewed, and whether it was necessary to conduct a wider or more systematic audit of their work. Some delegates thought that this process would be helpful and could be used to evaluate whether there were conflicts of interest or particular complaints about the way a committee functioned. However, others felt that it would add an extra level of unnecessary bureaucracy for members of RECs and could lead to further delays. It was suggested that it might be useful to consider a mechanism for accreditation of RECs. Alternatively, the standards set out by WHO (paragraph 5.21) could be used as the basis for internal review. The RECs could also be audited by local regulatory authorities or international bodies.

Summary of discussion about ethical review

5.25 All agreed that the ethical review of research played a crucial role in protecting research participants. The fact that the process in the host and sponsor countries was beset by a number of problems, ranging from logistical delays to more substantive differences of opinion that could not be resolved by consultation with the guidance, was a major concern.

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14 World Heath Organization (2000) *Operational Guidelines for Ethics Committees That Review Biomedical Research* (Geneva: WHO).

15 WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; EU 2001, Article 3.

16 CIOMS 2002, Guideline 2.

5.26 Several themes emerged throughout the Workshop:

- RECs have a duty to ensure adequate review of both ethical and scientific aspects of research proposals.
- In order to realise the benefits of ethical review, the process needs to be made much more efficient.
- Innovative methods of collaboration could be used to improve communication between different RECs, particularly between committees in the host and sponsor countries.
- Responsibilities might be devolved between committees. For some issues, the local expertise of the host REC is crucial.
- RECs in developing countries face serious difficulties through a lack of funding and a need to maintain independence.
- A particular problem is a lack of expertise among members of RECs. Initiatives to develop expertise in ethical review, through training and capacity building, are crucial.
- There were concerns that requiring a REC to monitor research after it had begun would increase the already burdensome workload of RECs.

Chapter 6

General themes

General themes

6.1 The issues raised by consent, standards of care, post-trial access to treatment, and ethical review in externally sponsored research are interrelated, and decisions reached in one of these four areas will often have a bearing on discussion about another. Clearly, all four areas need to be considered together in the design of a research proposal. During the Workshop discussion, some common themes were identified that cut across several aspects of research. In this chapter we discuss these general themes and examine the way that they are addressed in the guidance. The themes identified include:

- innovative ways of encouraging community participation in research;
- development of expertise;
- sustainability;
- partnership; and
- ensuring feedback from research.

We then turn to a number of related issues that were discussed briefly at the Workshop. These are not given much attention in the guidance (see Appendix A), but would merit further discussion and debate. They concern:

- increasing awareness of chronic diseases;
- research on public health; and
- intellectual property.

We then discuss national priorities for research, which are increasingly recognised as a critical determinant of whether research proposals should be supported. Finally, in the light of the experiences and evidence discussed during the Workshop, we consider the practical experience of implementation of guidance in healthcare-related research.

Innovative ways of encouraging community participation

6.2 The importance of involving the wider community in externally sponsored research is already explicitly addressed in general terms in some of the guidance.[1] Throughout the Workshop, delegates emphasised the need for community participation when conducting research in developing countries. However, it was acknowledged that defining a 'community' was rarely straightforward and researchers might sometimes not be aware of the diverse interests of different members of a given community. In addition, divisions within a community, or competing pressures could make it difficult to reach agreement about health issues.

6.3 Bearing these limitations in mind, engagement with the community was seen to have two main roles. First, involving the community helped researchers and sponsors to develop and maintain trust in a research project. Secondly, local consultation provided a means of adapting research designs for use in particular communities. For example, it had been noted that the establishment of Community Advisory Boards in the HapMap project (see Box 6.1) and educational initiatives

[1] For example, CIOMS 2002 acknowledges the importance of ethics review committees having a thorough understanding of a community's customs and traditions, and recommends that the committee should have either members or consultants with such an understanding (Commentary on Guideline 3); it also recommends that 'sponsors and investigators should develop culturally appropriate ways to communicate information' (Commentary on Guideline 4). CoE 2004 states that the existence of an independent ethics committee ensures that the interests and concerns of the community are represented (Explanatory Report, paragraph 41). Other guidance, such as the WMA 2000 and EGE 2003, does not address the issue.

in the KAVI vaccine trials in Kenya (see Box 2.5) had improved awareness of the research in local communities. In the case of the consent process, community involvement could facilitate the provision of information to participants (see paragraphs 2.14–2.15 and Box 2.5), and discourage inappropriate inducements. The role of the community was also highlighted in discussion about the provision of post-trial treatment and ethical review of research. There was agreement that, wherever possible, lay members should participate in the review process.[2]

Box 6.1: **Engaging with the community – Community Advisory Boards in the HapMap project (case study contributed by Professor Charles Rotimi)**

The International HapMap Project aims to determine common patterns of variation in DNA sequences in the human genome and to make this information freely available in the public domain (see also Box 2.6). An international consortium will collect DNA samples from populations in Africa, Asia and Europe.

The importance of genuine engagement with the community has been recognised at all stages of the project. In Nigeria, communities were given an opportunity to share their views through a range of individual interviews, focus groups and community meetings before the project began. A survey was also conducted to assess community attitudes, beliefs and experiences, and participants were invited to comment on the way in which samples would be collected.

In addition, a Community Advisory Board (CAB) was established in July 2003, to provide continuing community review and oversight of the project. There are nine members, and the Chair and other positions were selected by an open and democratic process. The Coriell Institute for Medical Research, the sample repository, will provide up to US$1,000 per year to defray associated expenses, and the CAB will hold periodic meetings. The CAB will liaise with Coriell to check that future uses of the samples are consistent with the uses described in the consent documents. The CAB will also continue to monitor engagement with the community, and public consultation to ensure that initiatives do not cease when the collection of samples is completed.

US$50,000 was allocated by the project to initiatives to encourage engagement with the community. Those involved considered that the process has raised the standard of research. However, questions were posed as to whether other studies would be able to afford a commitment of this nature.

See The International HapMap Consortium (2003) The International HapMap Project *Nature* **426**: 789–96; The International HapMap Consortium (2004) Integrating ethics and science in the International HapMap Project *Nature Reviews Genetics* **5**: 467–75.

Development of expertise

6.4 The importance of strengthening local expertise in research while conducting externally sponsored research was also highlighted throughout the Workshop. Guideline 20 of CIOMS 2002 states that sponsors and investigators have an obligation to contribute to national and local capacity in biomedical research[3] (see Appendix A, Table 4). NCOB 2002 accords responsibility to sponsors by suggesting that they require the development of local expertise in research to be included as an integral component of research proposals.[4] The guidance of the MRC of South Africa also explicitly emphasises the need for the development of

2 CoE 2004 emphasises the importance of having lay members on an ethical review committee (Article 9).

3 'In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects… contribute effectively to national and or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.' CIOMS, 2002, Guideline 20.

4 NCOB 2002, paragraph 9.52.

infrastructure and research capacity to be addressed before research is completed.[5]

6.5 Delegates took the view that all externally sponsored research had the potential to provide opportunities to increase the number of qualified scientists and to improve the skills of professionals. For example, in Fiji, there was often interest from external researchers to conduct projects investigating human genetics in local populations. Many of these projects, such as the investigation of the genetic basis for colour blindness, were unlikely to have immediate relevance to the local population or nationally defined priorities. However, they received approval from the local REC on the condition that a local researcher was included in the study, and the sponsor contributed to the strengthening of expertise during the project (see also paragraph 6.21). Delegates emphasised that researchers in developing countries needed to be actively involved in planning research and not merely responsible for implementing protocols initiated by foreign partners.

6.6 Delegates concluded that both researchers and sponsors should share responsibilities for strengthening expertise, and that partnerships to assist efforts to develop regional and national capacity should be established wherever possible. Sponsors could also support training programmes. For example, substantial progress has been made in the past few years in strengthening expertise in research on malaria through the activities of the African Malaria Network Trust (AMANET), which has run workshops in Good Clinical Practice, data management and research ethics. The Fogarty International Center and the Wellcome Trust also support research and training with a series of grants and programmes. As mentioned previously, the development of expertise in ethical review is urgently required (see also paragraphs 5.17–5.21).[6]

Sustainability

6.7 The importance of longer term considerations, including the sustainability of local healthcare facilities strengthened through externally sponsored research, was also emphasised. Local improvements needed to be planned so that they were sustainable once research was complete. One example cited was the AIDS Support Organisation (TASO) clinic in Entebbe, Uganda, where trials of a pneumococcal vaccine were conducted. The research infrastructure was subsequently used for trials of anti-retroviral treatments and the research activities also had a beneficial effect on improving the standard of routine care at the clinic.

6.8 The need for sustainability of health-related improvements is recognised in CIOMS 2002, which advises that 'the development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of research'.[7] NCOB 2002 also suggests that the sustainability of any changes introduced for the purposes of research should be considered. However, improvements are usually financed from research funds and are unlikely to be sustainable by this means once the research is completed. As the Report comments, 'much ill-feeling may be generated and further research in the particular community compromised, if, at the end of the study, the researchers leave and the improvements to healthcare are not sustained'.[8] Delegates acknowledged that, in practice, it was often not possible for an institution to maintain improvements in the longer term. However, other achievements in developing expertise, whether of personnel, of attitudes or of infrastructure, may contribute towards sustainability.

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5 Medical Research Council of South Africa (2002) *Book 1 Guidelines on ethics for medical research: General principles* (SA MRC), paragraph 11.4.4i.

6 Recent training initiatives include the International Research Ethics Network for Southern Africa (IRENSA), which offers a programme to train students in international research ethics in order to support RECs.

7 CIOMS 2002, Commentary on Guideline 10.

8 NCOB 2002, paragraph 9.10.

Partnerships

6.9 NCOB 2002 stressed that the context for externally sponsored research is one of considerable inequalities of power and advantage between developing and developed countries.[9] A fundamental moral principle identified in this regard is that the more powerful have a duty to refrain from exploiting the vulnerability of the weaker. Furthermore, in order to avoid erosion of the principle in practice and to avoid unfairness, it is important for the duty to be observed uniformly by all individuals and organisations.

6.10 A recurring theme at the Workshop, reflecting support for this approach, was the crucial importance of discussion between the stakeholders in research. As one delegate commented, 'the whole research endeavour should be created as a partnership'. Researchers, sponsors, participants, the local community and the local health authorities should work in partnership before research begins. They should consider the importance of the research questions, procedures for obtaining consent, the provision of an appropriate standard of care, and the sustainability of arrangements once research is complete. The crucial nature of partnership in the research setting is recognised in some of the guidance.[10] NCOB 2002 considers that promoting genuine partnerships between researchers in developed and developing countries should help to strengthen expertise in research and maximise the opportunity for the transfer of knowledge and skills.[11]

Ensuring feedback from research

6.11 The need to make research findings available after research has been completed is also encouraged by the guidance.[12] WMA 2000 and EGE 2003 both specify that negative as well as positive results should be included. Delegates emphasised the importance of making research results available to local health authorities so that decisions could be made about healthcare in the future. How such information is provided to the community will vary according to the circumstances. NCOB 2002 suggests that a public meeting may be an appropriate forum.[13]

6.12 Providing feedback to individual participants in research would also help to strengthen a sense of partnership. Delegates commented that failure on the part of researchers to do so is a frequent reason for reluctance to participate in any subsequent research. However, CoE 2004 also recognises that the wishes of a participant *not* to receive information should be recognised and that, where appropriate, results should also be provided within a framework of healthcare or counselling.

Increasing awareness of chronic disease

6.13 Delegates observed that discussions about research in developing countries are often overly influenced by issues arising from clinical trials and research to investigate infectious diseases.[14] However, the burden of chronic non-communicable disease (NCD) in developing

9 NCOB 2002, paragraphs 2.32, 4.19 and 10.10.

10 EGE 2003, paragraph 2.4: 'The involvement of all partners, from the funding institutions to the host countries or communities, is essential at each phase of the research activities, from the definition of the programme and of the research priorities, to the follow-up after the end of the trials. The involvement of local scientists from the host country at the very early stage of the planning and implementation … is crucial to develop a culture of collaboration. Their knowledge of local conditions and traditions is also necessary to identify local needs.'

11 NCOB 2002, paragraph 10.50.

12 WMA 2000, paragraph 27; CIOMS 2002, Items 34 in Appendix 1 Items to be included in a protocol … for biomedical research involving human subjects; CoE 2004, Articles 26–28; EGE 2003, paragraph 2.14; NCOB 2002, paragraph 9.40.

13 NCOB 2002, paragraph 9.40.

14 CIOMS 2002 acknowledges that trials to test vaccines and medicinal drugs 'constitute a substantial part of all research involving human subjects' (Preamble).

countries is increasing and will require more research in the future. NCDs, including cancer, diabetes, cardiovascular disease, chronic respiratory disease, and mental health disorders, currently account for almost half the global burden of disease. Moreover, the majority of deaths, disability and morbidity resulting from NCDs take place in low- and middle-income countries.[15]

6.14 There was general agreement that the guidance needed to give greater attention to research involving chronic diseases requiring long-term treatment, including those with infectious aetiology, such as HIV/AIDS. The need for long-term provision of any treatment that might be available after a trial is over poses particularly difficult questions in some settings.

Research on public health

6.15 There was also debate at the Workshop about whether sufficient consideration has been given in the guidance to research concerned with public health. Here, the best interests of research participants have to be balanced against the best interests of the community as a whole. The guidance emphasises clinical research, with particular focus on trials of new medicines or vaccines. However, many different types of research related to healthcare in developing countries involve public health, such as epidemiology, surveillance studies, and operational research.

6.16 For example, in deciding whether to introduce a new vaccine into a public health programme, there will be a need to know not only whether the disease is prevented but also the level of protection which is provided. It may therefore be important to continue a research trial not only until a positive effect is established but until there is a good estimate of the level of protection. In these circumstances, those in the group who have not received the vaccine may be disadvantaged. However this approach can provide public health authorities with the information necessary to make the best decision on the future use of the vaccine for the community as a whole.

6.17 The ambiguity of the division between research and the practice of public health was reflected in discussion at the Workshop. For example, a distinction is often made between research and surveillance; surveillance activities are sometimes classified as not requiring ethical review as they are a component of public health practice. However, they often have a research component. The WHO/UNAIDS Surveillance Working Group has recently commissioned a Paper on ethical issues in second generation surveillance.[16] Published in April 2004, it sets out a number of guidelines, although it does not reflect official policy of WHO or UNAIDS. This document recommends that all surveillance activities should be subject to a process of wide ranging consultation with the community and to ethical review. It recognises the particular difficulties that are associated with the HIV epidemic, when people thought to be at risk or who are in fact at risk may be subject to stigmatisation, discrimination and violence. The authors conclude that as a result, confidentiality has assumed critical importance in the conduct of surveillance. The obligation to disseminate data and the right of participants to access test results is also emphasised.

6.18 CIOMS, recognising the tensions and 'special features' of epidemiological research, published *International Guidelines for Ethical Review of Epidemiological Studies* in 1991

15 World Health Organization *Noncommunicable Diseases and Mental Health Cluster*. Available: http://www.who.int/noncommunicable_diseases/en Accessed on: 2 Feb 2005.

16 Fairchild AL and Bayer R (2004) *Ethical issues to be considered in second generation surveillance* commissioned by the WHO/UNAIDS Surveillance Working Group. Available: http://www.who.int/hiv/pub/epidemiology/sgs_ethical/en/ Accessed on 2 Feb 2005.

(Epidemiological Guidelines).[17] They address issues of consent, recommending that individual consent should be obtained together with agreement of a community representative. However, they acknowledge that obtaining individual informed consent may not always be practical and some flexibility may be required. For example, in some community-based randomised trials, whole communities are categorised randomly as to whether or not they receive an intervention. Ethical review is also required for all epidemiological studies. The 1991 Epidemiological Guidelines state that, during the ethical review process, 'there is a responsibility to ensure that the Declaration of Helsinki and CIOMS guidelines are taken into account in epidemiological studies'.

6.19 CIOMS 2002 addresses issues of confidentiality of data and use of biological samples, with specific mention of epidemiological studies. The commentary to Guideline 18 acknowledges that 'it is usually impractical to obtain the informed consent of each identifiable patient [in epidemiological studies]; an ethical review committee may waive the requirement for informed consent … provided that there are secure safeguards of confidentiality'. Issues concerning research related to public health are not specifically addressed in other guidance, much of which relates to clinical trials for medicinal products.[18]

Intellectual property

6.20 Large-scale studies in genetic epidemiology are being conducted in several different populations, including The Gambia, Ghana, Kenya, Malawi, Mali, and Vietnam. One aim is to examine the extent to which susceptibility to malaria is determined by genetic variation in the human immune system. Because there are a number of complex interacting factors, very large sample sizes are needed from a range of different populations.

6.21 This form of research raises questions about benefit sharing. One of the main issues in the debate on access to genetic resources in developing countries concerns the relationship between intellectual property protection and the ownership and rights pertaining to the resources on which the intellectual property right has been based. Only recently has the international community sought to recognise and protect genetic resources though international agreements such as the Convention on Biological Diversity.[19] The principles of benefit sharing and equitable access to genetic resources are widely accepted but remain difficult to implement. For example, what should happen if a gene that offers some protection against malaria is discovered in one specific community but not others? If a product is developed based on this finding, should only members of the community in which the gene was discovered benefit, or should all communities who were involved in the research benefit equally, and if so, how should they benefit? Furthermore, there are various stakeholders involved in research including participants, health professionals, epidemiologists, geneticists, and companies, who may all have an interest. It was suggested that arrangements for possible benefits should be based on a partnership between sponsors and researchers both in the sponsor and local country. Further discussion of these issues was set aside as they were beyond the scope of the Workshop. However, they will clearly require attention in the future.

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17 The 1991 Epidemiological Guidelines took into account the proposed draft of the CIOMS International Guidelines for Biomedical Research Involving Human Subjects, produced in 1982. These guidelines are currently under revision in order to ensure they complement the most recent revision, CIOMS 2002.

18 CoE 2004 covers the 'full range of research activities in the health field involving interventions on human beings', where 'intervention' includes a physical intervention and any other intervention in so far as it involves a risk to the psychological health of the person concerned (Article 2). The Explanatory Report suggests this should be taken to include questionnaires, interviews and observational research, and genetic epidemiology (paragraph 17).

19 Commission on Intellectual Property Rights (2002) *Integrating Intellectual Property Rights and Development Policy* (London: CIPR).

Setting research priorities

6.22 National resources for research in developing countries are generally very limited and setting priorities for healthcare-related research is therefore crucial. The more a country can determine its own priorities and conduct its own research, the easier it will be to ensure that research proposed by external sponsors is appropriate and relevant to its national health needs. Those elements of the guidance (WMA 2000, CIOMS 2002, EGE 2003 and NCOB 2002) that address the issue of setting research priorities generally agree that populations should benefit from research undertaken in their community.[20] EGE 2003 emphasises that research protocols should be relevant to national health priorities.[21]

6.23 With regard to the question of how this might be achieved, CIOMS 2002 states that the health authorities of the host country should ensure that the proposed research is responsive to the health needs and priorities of that country.[22] It also considers that national or local ethical review committees 'have a special responsibility' in this area.[23] Delegates considered the role of the research ethics committee should be as a 'gate-keeper' rather than to set research priorities. However, they affirmed that developing countries should have a mechanism to set research priorities for healthcare, to enable, *inter alia*, effective collaboration with external sponsors.[24] NCOB 2002 recommends that all countries should set priorities for research into healthcare.[25]

6.24 The Millennium Development Goals (MDGs), adopted by 189 nations in the United Nations Millennium Declaration in September 2000, have provided an additional source of priorities. Specific goals address the need to reduce child mortality, improve maternal health, and aim to halt and begin to reverse the incidence or spread of HIV/AIDS, malaria and other diseases. However, delegates observed that adhering only to the MDGs may divert scarce resources from other priorities which may be as, or even more important in specific settings. Setting priorities at a national level was therefore considered to be crucially important.

6.25 Once diseases have been identified as a national priority for research, what kind of programmes should be implemented? For example, if malaria is specified as a priority, what types of research would be acceptable? Should basic research, clinical research, vaccine trials, intervention studies and operational research all be given equal priority, or should some types of research be given more emphasis? These questions were beyond the scope of the Workshop but clearly need to be addressed in future discussions.

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20 NCOB 2002 states: 'research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committees why the research should be carried out if this is not thought possible' (paragraph 9.49). Similar provisions can be found in CIOMS 2002, Guideline 10; EGE 2003, paragraph 2.13 and National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 4.3: 'Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.'

21 EGE 2003, paragraph 2.9.

22 CIOMS 2002, Guideline 3.

23 CIOMS 2002, Commentary on Guideline 3.

24 The Council for Health Research for Development (COHRED) has published guidance on priority setting, including *Essential National Health Research* (ENHR), an integrated strategy for organising and managing health research in different countries. The Global Forum for Health Research has also reviewed methodologies for priority setting and the most recent report (Global Forum for Health Research (2004) *The 10/90 Report on Health Research 2003-2004* (Geneva: GFHR) includes a detailed analysis of the various approaches to setting research priorities.

25 NCOB 2002, paragraph 2.31.

Implementing guidance

6.26 A survey of researchers at the Workshop suggested that they refer primarily to national and institutional guidelines when designing research protocols.[26] However, there is a wide range of other guidance and researchers are often uncertain about which of these documents need to be considered. The degree to which standards demanded by documents such as WMA 2000 *must* be achieved, and the degree to which they might be regarded as aspirational is also not always clear.

6.27 Most of the guidance we have discussed in this Paper, with the exception of CoE 2004, does not have the force of law (see Table 1.1)[27]. However, some of the documents still have very real implications for policy and practice of healthcare-related research, as a Resolution, Declaration or voluntary code of practice often carries significant weight and influences policy makers who devise binding legislation. The Declaration of Helsinki (WMA 2000), for example, is widely regarded as the pre-eminent ethical guidance on healthcare-related research.[28] Its provisions are referred to in regulations governing research involving human participants. For example the EU Directive 2001/83/EC *on the Community code relating to medicinal products for human use* refers to the Helsinki Declaration, stating 'All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki.'[29] Similarly, many organisations and companies sponsoring research will frequently only provide funding if researchers abide by the requirements set out in WMA 2000. Even though it is not a regulatory device, it has far more influence than a document that merely formulates aspirational ideals.

6.28 However, questions remain about the duties that the Declaration imposes on researchers, sponsors and others. Are its terms non-negotiable or is some flexibility implied by its status as a declaration that is not directly legally binding? On one view, its provisions might be seen to be immutable and demanding standards that must apply in all circumstances regardless of resources and welfare considerations. Indeed, these are effectively the terms in which the Declaration sets out its primacy:

> '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.'[30]

On another view, the Declaration might be seen to be aspirational in its aims, setting out ideals that may not be attainable by all in all circumstances, but which are nevertheless crucial in setting standards. As one delegate put it:

"We are aware that we do not always achieve perfection, but the guidelines provide useful ideals for us to aim towards."

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26 The survey of the delegates' views was conducted by the Wellcome Trust in May 2004 as part of a consultation about the Trusts' draft Position Statement for Wellcome Trust funded research involving human participants in developing countries.

27 The Protocol is only binding for those countries that have signed and ratified it, and are party to the 1997 Convention on Human Rights and Biomedicine.

28 Taking into account the Nuremberg Code, the WMA, the international professional association of physicians, developed the Declaration of Helsinki to help prevent any abuse of trial participants. In the years that followed, as national governments and a wide range of other organisations developed legislation and codes of practice to protect human subjects in research, the Declaration was an obvious and appropriate starting point.

29 EU Directive 2001/83/EC, Annex I part 4 (B).

30 WMA 2000, paragraph 9.

In this regard it is noteworthy that the WMA Workgroup established to consider the revisions of paragraph 30, explored the option of adding the following preamble '… explaining that the Declaration is a set of ethical guidelines, not laws or regulations':

> 'As a statement of principles, the Declaration of Helsinki is intended to establish high ethical standards that guide physicians and other participants in medical research involving human subjects. These ethical principles provide the basis of moral reflection on the means and goals of research involving human subjects, distinct from national legal and regulatory requirements. Interpreting the provisions of the Declaration regarding the design, conduct or completion of the research requires careful balancing of all of the Declaration's ethical principles. Differences in interpretation should be resolved by physicians and other participants involved in the research who are most familiar with all relevant factors, including the needs of research participants and of the host population.'[31]

In the event, the preamble was not adopted and a Note of clarification was added to paragraph 30 (see also Box 4.1).

6.29 Other guidelines that have followed WMA 2000 have sought to interpret its articles to provide clarification for researchers, sponsors and others. For example, the CIOMS 2002 Guidelines seek to explain and develop WMA 2000, particularly in the context of research in developing countries. Sponsors including the UK MRC, the Wellcome Trust and the National Institutes of Health (NIH) have prepared guidelines specifically for those conducting externally sponsored healthcare-related research.[32] These various guidelines have made an important contribution to the protection of human participants in that they have not only developed the guidance as a whole, but have also encouraged debate and raised awareness of the issues raised by research. However, the variability of the guidance across a range of issues is likely to continue to place those wishing to conduct research in developing countries in a quandary.

6.30 Some principles set out in international guidance, such as the need for individual consent to participate in research, have been endorsed as universal, although community randomised trials may provide an exception (see paragraph 2.8). However, other provisions in WMA 2000, such as those dealing with the standard of care that researchers and sponsors should provide to the control group during research, have been viewed as being too narrowly construed, and CIOMS 2002, CoE 2004 and NCOB 2002 accept different provisions.[33] Some of the differences may be attributable to variations in the scope and legal status of the guidelines. Nevertheless, the lack of consistency between different elements of the guidance, particularly between CIOMS 2002 and WMA 2000, is regrettable, especially in the developing country context where the risk of exploitation of vulnerable populations is significant. Would a decision by physicians involved in a trial to forgo the obligation to provide treatment to participants after the trial is over, as specified by WMA 2000 and EGE 2003, and follow instead the more flexible approach advocated by CIOMS 2002 and NCOB 2002, leave the sponsor open to criticism?

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31 World Medical Association (2004) *Workgroup Report on the revision of paragraph 30 of the Declaration of Helsinki*. Available: http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf Accessed on: 3 Feb 2005.

32 Medical Research Council (2004) *MRC Ethics Guide: Research involving human participants in developing societies* (London: MRC); Wellcome Trust (2005) *Wellcome Trust Funded Research Involving People Living in Developing Countries* (London: Wellcome Trust); NIH (1997) *Guidelines for the conduct of research involving human subjects at the NIH* (5th Printing August 2004) (Washington, DC: NIH).

33 CIOMS 2002, Introduction and Commentary to Guideline 11; CoE 2004, Explanatory Report, paragraph 120; NCOB 2002, paragraphs 7.29–7.30.

6.31 It was apparent at the Workshop that the complexity experienced by researchers in the field is inevitably not addressed in the guidance. Difficulties in formulating general guidance that will apply in all circumstances are unavoidable. However, critics argue that in the absence of consistency between different guidelines, researchers and sponsors can simply select those that best suit their purposes.

6.32 In such situations, the formulation of national guidance assumes particular importance. By developing its own national guidance, a developing country is able to take account of its particular needs and cultural context. In NCOB 2002, the Council recommended that developing countries should be encouraged 'to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application'.[34] The availability of such guidance provides a basis for sponsors and researchers to design research that takes account of local circumstances. A rigorous and effective process of ethical review is also crucial to assess the appropriateness of the proposed research.

6.33 Much progress has been made over the past few years in the development of national and international guidance and the strengthening of capacity for ethical review in developing countries. However, researchers, sponsors and governments need to be clearer how guidance is to be understood, and how it is interpreted in practice. Differences or ambiguities between guidelines may lead to unnecessary delays or even inhibit much needed research. As one delegate commented:

> *"Ethical and scientific uncertainties should not paralyse us but incite us to make more progress."*

6.34 It is important to learn from experience. The Workshop provided the opportunity to consider specific examples and this proved to be a worthwhile approach. It may become easier to justify a change in the way ethical principles are applied when there is clear evidence that the approach that was previously advocated had harmful, and perhaps unexpected, consequences. For this reason alone it can be very helpful to review the situation every few years, as this Paper has attempted to do. New evidence, or new ideas, may indicate the need for a change in approach.

34 NCOB 2002, paragraph 5.28.

Appendices

Appendix A: Comparison of guidance on research related to healthcare in developing countries

Table 1: Guidance relating to consent

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 22	*Provision of information:* Participants 'must be adequately informed about: • the aims and methods of the study; • the sources of funding and possible conflicts of interest; • the institutional affiliations of the researcher; • the anticipated benefits and potential risks; • the discomfort it may entail; and • the right to abstain from taking part in the study, or to withdraw from it at any time without reprisal.' [Paragraph 22] *Recording consent:* Written consent is preferable but 'non-written' consent can be acceptable in some cases: '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.' [Paragraph 22] *Other points:* Paragraph 23 addresses the process of obtaining consent 'if the subject is in a dependent relationship with the physician or may consent under duress.' Paragraphs 24–26 consider how consent should be obtained when potential participants are legally incompetent, physically or mentally incapable of giving consent or for children.
CIOMS 2002	Guidelines 4 - 7	*Individual informed consent* 'For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law.' [Guideline 4]
		Who should give consent? Community consent may be required but should never replace individual consent. 'In some cultures an investigator may enter a community to

Continued

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent.' [Guideline 4, Commentary] *Provision of information:* 'Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand', then lists 26 items including aspects of the design of the trial (randomisation, double blinding); possible health risks for participants, and treatment options; issues relating to data protection; and questions of liability in the case of disability or death resulting from injury related to the research.' [Guideline 5] The commentary on Guideline 4 also addresses the importance of the 'process' of obtaining consent. *Recording consent:* 'Consent may be indicated in a number of ways. The subject may imply consent by 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.' [Guideline 4, Commentary] *Waiving consent:* 'Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.' [Guideline 4] '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. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (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. [Guideline 4, Commentary] *Continued*

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	*Inducements:* 'Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, 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 provided to research subjects must have been approved by an ethical review committee.' [Guideline 7]
CoE 2004	Article 13, 14	*Who should give consent?* Individual consent required: 'No research on a person may be carried out… without the informed, free, express, specific and documented consent of the person.' [Article 14] *Provision of information:* Article 13 lists the information that should be addressed during the consent process: 'Persons being asked to participate in a research project shall be given adequate information in a comprehensible form… [covering] the purpose, the overall plan and the possible risks and benefits of the research project: i. of the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project; ii. of available preventive, diagnostic and therapeutic procedures; iii. of the arrangements for responding to adverse events or the concerns of research participants; iv. of arrangements to ensure respect for private life and ensure the confidentiality of personal data; v. of arrangements for access to information relevant to the participant arising from the research and to its overall results; vi. of the arrangements for fair compensation in the case of damage; vii. of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials; *Continued*

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CoE 2004	Article 13, 14	viii. of the source of funding of the research project. … and their right to refuse consent or to withdraw at any time without being subject to any form of discrimination.' [Article 13] Methods of providing the information are also discussed in the Explanatory Report, paragraph 72. *Recording consent:* Consent must be documented. 'Express consent may be either verbal or written as long as it is documented. Best practice demands that written consent be obtained, except in exceptional circumstances.' [Explanatory Report, paragraph 79] *Inducements:* Details of all payments and rewards to be made in the context of the research project must be considered by the ethics committee. [Appendix: Information to be given to the ethics committee] *Other points:* Article 15 discusses protection of persons not able to consent to research; Article 19 discusses research in emergency clinical situations, when a person is not in a state to give consent.
EU 2001	Article 3.2	*Who should give consent?* Individual consent is required: 'A clinical trial may be undertaken only if: …(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial.' [Article 3.2 d] *Provision of information:* 'A clinical trial may be undertaken only if, in particular: the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time.' [Article 3.2 b]

Continued

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 3.2	*Recording consent:* Verbal consent may only be obtained if the participant is illiterate: '…if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.' [Article 3.2 d] *Other points:* Opening paragraphs (3) and (4) discuss the involvement of persons incapable of giving legal consent in clinical trials. Article 4 discusses consent for research involving minors, and Article 5 discusses trials on incapacitated adults not able to give informed legal consent.
EGE 2003	Paragraph 2.7	*Who should give consent?* Consent of family or community leader may be required in addition to individual consent: 'The involvement of people with knowledge of the local conditions and traditions and able to defend the interest of those affected by the project is necessary to guarantee the most appropriate procedures of informing of the potential participants in a clinical trial. According to the local situation, it may be appropriate to seek agreement on the implementation of a research project from persons representative of or invested with a certain authority within the community, or the family. However, free and informed consent always has to be given by each individual involved in a trial.' [Paragraph 2.7] *Recording consent:* Does not indicate how consent should be best recorded.
NCOB 2002	Chapter 6	*Who should give consent?* Consent of senior family member or community leader may be required in addition to individual consent: 'We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected.' [Paragraph 6.22, and discussion 6.18-6.22]

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Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 6	*Provision of information:* 'Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given.' [Paragraph 6.40, and discussion 6.4–6.17] *Recording consent:* Verbal consent is acceptable only if written consent is inappropriate: 'Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent.' [Paragraphs 6.37-6.40] *Inducements:* 'We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.' [Paragraph 6.32, and discussion 6.25–6.32] *Other points:* Uses concept of 'genuine consent' instead of 'informed consent':[1] 'Ensuring that consent is genuine requires care in detecting a lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what has been proposed, lack of disclosure of material facts, or conflicts of interest. To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made.' [Paragraphs 6.4-6.5]

[1] The concept of genuine consent was introduced by the NCOB in its 1995 Report, *Human Tissue: Ethical and Legal Issues*, paragraph 6.20.

Table 2: Guidance relating to standards of care

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 29	*The standard of care that should be provided to the control group during research:* '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.' [Paragraph 29] *The use of placebos:* Placebos may be used only 'for compelling and scientifically sound methodological reasons' or when the risks to the participant and the condition being studied are minor. A 'Note of clarification on Paragraph 29 re. the use of placebos' was published in December 2002: 'The WMA reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available under the following circumstances: - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the participants who receive placebo will not be subject to any additional risk of serious or irreversible harm.' [Note of clarification on Paragraph 29]
CIOMS 2002	Guideline 11	*The standard of care that should be provided to the control group during research:* 'As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or 'no treatment'.' [Guideline 11] New terminology was introduced in 2002: 'established effective intervention' used as a term for reference treatment, to include all current interventions, 'including the best and the various alternatives to the best.' [Introduction]

Continued

Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 11	*The use of placebos:* 'Placebo may be used: • when there is no established effective intervention; • when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; • when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.' [Guideline 11] The commentary to Guideline 11 discusses the specific cases when the use of a placebo in place of an 'established intervention' may be morally justified. For example, a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, may seek to develop an affordable intervention specifically for a health problem affecting its population. 'Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country.' [Guideline 11, Commentary]
CoE 2004	Article 23	*The standard of care that should be provided to the control group during research:* 'Research shall not deprive participants of necessary procedures… In research associated with prevention, diagnosis or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment.' [Article 23.2] 'It is expected that a proven method of treatment that is available in the country or region concerned be utilised.' [Explanatory Report, paragraph 120] *The use of placebos:* 'The use of placebo is permissible where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden.' [Article 23.3]

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Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 19	Does not address placebo-controlled trials or standard of care issues. *The obligations of sponsors:* 'Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration should be made available free of charge by the sponsor.' [Article 19]
EGE 2003	Paragraph 2.10, 2.12	*The use of placebos:* 'The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost. It may thus be justified to derogate from the rule of best proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.' [Paragraph 2.10] It should be noted that 'two members of the Group recorded their dissent, considering 'that the use of placebo for the purpose of developing low cost treatment could mean accepting a 'double standard' for poor and rich countries.' *The obligations of sponsors:* Where research participants would not receive a standard of care because of its cost, it must be provided by the sponsor: 'In industrialised countries, the reference treatment used in a clinical trial may be provided by the healthcare services, while the new drug being tested is provided by the sponsor. When a trial is implemented in a country or community where patients cannot benefit from the standard treatment because of the cost, it is then up to the sponsor to provide it.' [Paragraph 2.12] Paragraphs 1.24, 1.32, 1.34 and 2.10 also discuss the issues raised by the provision of different standards of care
NCOB 2002	Chapter 7	*The standard of care that should be provided to the control group during research:* Research below the universal standard of care can be justified in some cases. 'We recommend that in setting the standard of care for the

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Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 7	control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system.' [Paragraph 7.29] 'In exceptional circumstances, research may be proposed which involves the use of a standard of care that is lower than the best available intervention as part of the host country's public health system for the disease being studied. For example, researchers may wish to demonstrate that what is deemed to be the best treatment available through the host country's public health system is ineffective, or even harmful, by comparing it to a placebo, or an apparently lesser standard of care… If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.' [Paragraph 7.30] The Report also discusses standard of care as it relates to two more specific forms of research: (a) research into preventive measures; and (b) trials comparing different standards of care. *The provision of care to all trial participants:* 'We recommend that before research beings, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard deviation must be justified to the relevant research ethics committee.' [Paragraph 7.35]

Table 3: Guidance relating to what happens after the research is over

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 30	*Should post-trial treatment be provided?* 'At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.' [Paragraph 30] A Note of clarification on Paragraph 30 was issued on May 2004: 'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.' [Note of clarification on Paragraph 30] *Who should supply treatment or provide interventions?* Does not address who has an obligation to supply treatment.
CIOMS 2002	Guideline 10	*Who should supply treatment or provide interventions?* The sponsor should provide post-trial access to treatment: 'Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.' [Guideline 10] The commentary on Guideline 10 clarifies the concepts of 'responsiveness' and 'reasonably available', stating that sponsors and investigators should consult with relevant stakeholders of the country where the research is to take place, 'including the national government, the health ministry, local health authorities, concerned scientific and ethics groups, non-governmental organisations such as health advocacy groups, and representatives of the communities of those who might participate in the study.' [Guideline 10, Commentary] 'The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the *Continued*

Table 3: Guidance relating to what happens after the research is over *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 10	community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.' [Guideline 10, Commentary]
CoE 2004		Does not address the issue. The Appendix to the Protocol, which covers information to be given to the research ethics committee, does not stipulate that information about post-trial access to treatment is required or should be proved to participants during the consent process.
EU 2001		Does not address the issue.
EGE 2003	Paragraph 2.13	*Should post-trial treatment be provided?* Requires provision of successful treatment to all participants upon completion of the trial, even if treatment would need to be provided for a lifetime: 'In industrialised countries, free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal health care system. In developing countries, the same rule must be applicable even if this implies supplying the drug for a lifetime if necessary. Moreover, there should be an obligation that the clinical trial benefits the community that contributed to the development of the drug. This can be e.g. to guarantee a supply of the drug at an affordable price for the community or under the form of capacity building. The protocol of clinical trials must specify who will benefit, how and for how long.' [Paragraph 2.13] *Who should supply treatment or provide interventions?* However, EGE 2003 does not address who should be responsible for supplying treatment or maintaining relevant facilities.
NCOB 2002	Chapter 9	*Should post-trial treatment be provided?* Acknowledges that it may not be possible in all cases to ensure post-trial access and suggests that possible post-trial treatment options should be clarified before the trial begins: 'We endorse the 2001 National Bioethics Advisory Commission's (NBAC) recommendation that researchers should

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Table 3: Guidance relating to what happens after the research is over *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 9	endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.' [Paragraph 9.31] *Who should supply treatment or provide interventions?* Does not address who will supply treatment: 'Responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.' [Paragraph 9.36]

Table 4: Guidance relating to ethical review

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 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.' [Paragraph 13] Does not require a separate scientific review committee or discuss where review should take place.
CIOMS 2002	Guidelines 2, 3, 20	*Should there be separate scientific and ethical review?* Scientific review does not need to be performed by a separate review committee: '*Ethical and scientific review*: Committees in both the country of the sponsor 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.' [Guideline 3, Commentary] *Where should review take place?* While Guideline 2 discusses ethics review committees, Guideline 3 specifically addresses ethical review of externally sponsored research. Review should take place in both sponsoring and host country, although a host country is not always required to have a distinct fully functional REC in all cases: 'An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs *Continued*

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 20	and priorities of the host country and meets the requisite ethical standards.' [Guideline 3] 'When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol … The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research … However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.' [Guideline 3, Commentary] *Funding and support for a REC in the host country:* 'The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.' [Guideline 2] 'The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols, but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol.' [Guideline 2, Commentary] Sponsoring countries have a responsibility to support the building of capacity of RECs in developing countries. However, the guideline does not state whether this contribution should be provided to the host country directly or indirectly: 'Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.' [Guideline 20] *Continued*

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 20	'External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research.' [Guideline 20, Commentary] Recommendation 5.7 of the NBAC 2001 guidelines concurs: 'Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international and collaborative research.'[2] *Role of a REC after the approval of research:* 'The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.' [Guideline 2]
CoE 2004	Article 7, 9 – 12, 29	*Should there be separate scientific and ethical review?* Supports a scientific review of research protocols, by a 'competent body' (separate from discussion of ethical review): 'Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.' [Article 7] 'It is acknowledged that in some countries, the ethics committee could also act as the competent body while in other cases or in other countries, the competent body might be a Ministry or a regulatory agency, which would take the opinion of the ethics committee into account.' [Explanatory Report, paragraph 28] *Where should review take place?* Each State in which any research activity takes place should provide ethical review and an Appendix lists the information that should be given to the ethics committee for consideration: 'Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.' [Article 9] *Continued*

[2] National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC).

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CoE 2004	Article 7, 9 – 12, 29	Article 29 considers the possibility that research might take place in a country which is not a member of the Protocol, or in a country where no suitable body for the review of research exists. In such cases, the sponsors or researchers: 'shall ensure that, without prejudice to the provisions applicable in that state, the research project complies with the principles on which the provisions of this Protocol are based. Where necessary, the [sponsors and researchers] shall take appropriate measures to that end.' [Article 29] 'In addition to complying with all the conditions applicable in the State in the territory of which the research is to be undertaken, the principles on which the provisions of this Protocol are based must be complied with… For example, there may not be a body capable of undertaking appropriate independent scientific and ethical evaluation of research in the country, but the principle of the research project being submitted to an independent body for review must be observed this does not imply that a body in the state Party to the Protocol has the authority to approve research in the non-Party State if that State does not approve the research, or to override its regulations.' [Explanatory Report, paragraph 138] 'In the case where the research must be undertaken in States not having well established systems of protection, the provisions could foresee the obligation to submit the research project to an ethics committee of the Party concerned.' [Explanatory Report, Paragraph 140] *Funding and support for a REC in the host country:* 'Parties to this Protocol shall take measures to assure the independence of the ethics committee. That body shall not be subject to undue external influences.' [Article 10]
EU 2001	Article 3, 6, 9	*Should there be separate scientific and ethical review?* Implication that the ethics review should include both scientific and ethical review: 'The ethics committee shall consider… (a) the relevance of the clinical trial and the trial design… (c) the protocol…' [Article 6.3 a-c] *Where should review take place?* A single ethical opinion should be given by each state participating in the trial and a competent authority in the host country: *Continued*

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 3, 6, 9	'A clinical trial may be initiated only if the Ethics Committee and/or competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.' [Article 3.2 a] 'The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.' [Article 9] *Funding and support for a REC in the host country:* Discussion not necessarily related to trials outside EU countries, but states that: 'For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.' [Article 6.1]
EGE 2003	Paragraph 2.8	*Should there be separate scientific and ethical review?* EGE 2003 does not require a separate scientific review committee. Issues that should be considered during evaluation of a research protocol are listed in paragraph 2.9. *Where should review take place?* 'The scientific and ethical evaluation of the research protocol should be carried out by ethical committees from all countries involved. Host countries need to have a legal and ethical framework in order to take part in the clinical trial evaluation effectively and independently… When no local ethics committee exists, then the evaluation should be done by a mixed committee involving representatives from both EU Member States and host countries. It is essential that the members of this committee are independent and include persons representing participants' interests. If it is not possible to involve such an independent local representative in the evaluation, then no clinical trial should be implemented in the country.' [Paragraph 2.8] *Funding and support for a REC in the host country:* 'The group strongly supports EU initiatives to build local ethical committees in the host countries. It should be considered as a priority in terms of capacity building.' [Paragraph 2.8]

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Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 8	*Should there be separate scientific and ethical review?* A separate scientific committee should conduct a scientific review: 'There are concerns that, in a single ethics committee, the distinction between the review of the science and the ethics, which have quite different purposes, may be ill defined… We conclude that these two forms of review should, where possible, be kept separate. This may, but will not necessarily, require the establishment of separate committees.' [Paragraph 8.5] *Where should review take place?* Separate ethical reviews should take place in both countries: 'We recommend that externally sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted.' [Paragraph 8.22] 'all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.' [Paragraph 8.16] *Funding and support for a REC in the host country:* 'Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level.' [Paragraph 8.16] 'We conclude that there is a need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research.' [Paragraph 8.20]

Appendix B: Internet addresses of guidance

- **World Medical Association (WMA):**
  Declaration of Helsinki as last revised in Oct 2000; Notes of clarification on Paragraph 29 and Paragraph 30 added 2002 and 2004: http://www.wma.net/e/policy/b3.htm

- **The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO):**
  International Ethical Guidelines for Biomedical Research Involving Human Subjects, as last revised in Sep 2002; http://www.cioms.ch/frame_guidelines_nov_2002.htm

- **Steering Committee on Bioethics (CDBI) of the Council of Europe (CoE):**
  Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, adopted by the Committee of Ministers, June 2004;
  http://conventions.coe.int/Treaty/EN/Projets/Protocol-Biomedical%20research.htm#

- **European Council and European Parliament (EU):**
  Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, April 2001, adopted by Member States by May 2003, brought into force May 2004;
  http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf

- **The European Group on Ethics in Science and New Technologies (EGE):**
  Opinion Nr 17 on the ethical aspects of clinical research in developing countries, published in Jan 2003;
  http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf

- **Nuffield Council on Bioethics:**
  The ethics of research related to healthcare in developing countries, April 2002;
  http://www.nuffieldbioethics.org/developingcountries

Appendix C: Workshop programme and delegates

12–14th February 2004
Cape Town, South Africa

DAY ONE: Thursday 12th February

OPENING PLENARY		
9.00	**Welcome and introduction**	Professor William Pick *Acting President, SA MRC* Professor Sir Bob Hepple QC *Chairman of Nuffield Council on Bioethics*
9.15	**Comparison of guidelines** *Based on background paper*	Professor Sir Kenneth Calman KCB FRSE, *Nuffield Council on Bioethics and Chairman of the Working Party on the ethics of research related to healthcare in developing countries*
	Discussion	
SESSION I: CASE STUDIES		
10.00	**Acute disease** *Case study: malaria*	Speaker: Professor Malcolm Molyneux, *Wellcome Trust Unit, Malawi* Discussant: Dr Tumani Corrah *MRC Laboratories, The Gambia*
10.45	BREAK	
11.15	**Chronic disease** *Case study: developing guidelines for HIV vaccine trials in South Africa*	Speaker: Ms Catherine Slack, *HIV AIDS Vaccines Ethics Group (HAVEG), South Africa* Discussant: Professor Carlos Brites, *Head, Retroviral Laboratory, Federal University of Bahia, Brazil*
12.00	**Preventive treatments** *Case study: rotavirus vaccines*	Speaker: Dr Roger Glass, CDC, US Discussant: Dr Job Bwayo, *Kenya AIDS vaccine initiative, University of Nairobi, Kenya*
12.45	LUNCH	

SESSION II: BREAKOUT GROUPS I

2.00 Introduction — Professor Peter Smith, *London School of Hygiene and Tropical Medicine and Nuffield Council on Bioethics*

In-depth discussion of issues raised in guidance

2.15

1	2	3	4
Consent	**Standards of care**	**Once research is over**	**Ethical Review (including research priorities)**

Chairs: members of Steering Committee. Rapporteurs to be selected.
Feedback for each group will take place on Day Two.
BREAK between 3.30 – 4.00pm

SESSION III: PLENARY

5.15 **Research Priorities** — Speaker: Mr Tim Martineau, *Senior Health Advisor, DFID*

Discussant: Professor Terrence Forrester, *Tropical Medicine Research Institute, University of West Indies*

6.30 RECEPTION

DAY TWO: Friday 13th February

SESSION IV: BREAKOUT GROUPS II

9.00

1	2	3	4
Consent	**Standards of care**	**Once research is over**	**Ethical Review (including research priorities)**

In-depth discussion as on Day One. Delegates will take part in different Breakout Groups on each day.

BREAK between 10.45 – 11.15am

12.30 LUNCH

SESSION V: FEEDBACK FROM BREAKOUT GROUPS AND DISCUSSION

Chair: Professor Peter Smith

2.00	**Feedback: Consent**	Group I Rapporteur Group II Rapporteur Discussion
2.45	**Feedback: Standards of care**	Group I Rapporteur Group II Rapporteur Discussion
3.30	BREAK	
4.00	**Feedback: Once the research is over**	Group I Rapporteur Group II Rapporteur Discussion
4.45	**Feedback: Ethical review**	Group I Rapporteur Group II Rapporteur Discussion

DAY THREE: Saturday 14th February

SESSION VI: USER PERSPECTIVES

To discuss the impact of developments and revisions to guidelines for each of the three main user groups (researchers, reviewers and sponsors)

9.00	**Researchers**	Professor Jimmy Whitworth, *London School of Hygiene and Tropical Medicine* Dr Athula Sumathipala, *Director, Bioethics initiative, Forum for Research and Development, Sri Lanka* Discussion
9.30	**Ethical Reviewers**	Dr Asad Raja, *Chairman Ethics Review Committee, Aga Khan University* Dr Kim Mulholland, *Centre for International Child Health, Australia* Discussion
10.00	**Sponsors**	Dr Nadia Tornieporth, *Clinical Development Prophylactic Vaccines, GSK Biologicals* Dr Imogen Evans, *MRC* Discussion
	BREAK	

SESSION VII: NEXT STEPS		
	To explore areas which have not yet received significant discussion and to anticipate future developments	
11.15	Case study: **Collecting biological samples**	Professor Dominic Kwiatkowski, *Oxford University* Discussant: Dr Charles Rotimi, *HapMap, Nigeria*
12.00	Summing up and conclusion	Professor Catherine Peckham, *Nuffield Council on Bioethics* Professor Denie DuToit, *Chairman, SA MRC ethics committee*
	CLOSE OF WORKSHOP	
12.30	LUNCH	

List of delegates

Name	Organisation*	Country
Dr Angelica ANGELES	National Institute of Public Health (NIPH), Cuernavaca, Morelos	Mexico
Ms Gayane ASLANYAN	Armenian Drug and Medical Technology Agency	Armenia
Professor Solly BENATAR	International Research Ethics Network for Southern Africa (IRENSA), University of Cape Town	South Africa
Professor Zulfiqar BHUTTA	Professor of Paediatrics, Aga Khan University	Pakistan
Professor Carlos BRITES	Associate Professor of Infectious Diseases Head, Retrovirus Laboratory, Federal University of Bahia	Brazil
Dr Job BWAYO	Kenya AIDS Vaccine Initiative, University of Nairobi	Kenya
Professor Sir Ken CALMAN	Chairman of former Working Party on Ethics of research related to healthcare in developing countries, Nuffield Council on Bioethics, Vice-Chancellor and Warden, University of Durham	UK
Professor Alex CAPRON	World Health Organization	Switzerland

Continued

Name	Organisation*	Country
Dr Ayesha DE COSTA	Danida Assisted Madhya Pradesh Basic Health Services Program, Bhopal	India
Dr Tumani CORRAH	MRC Laboratories, Fajara	The Gambia
Dr Ames DHAI	SA MRC Ethics Committee Faculty of Health Sciences, University of Natal	South Africa
Professor Denie DU TOIT	Chair, SA MRC Ethics Committee	South Africa
Dr Imogen EVANS	Research Strategy Manager, Medical Research Council	UK
Professor Terrence FORRESTER	Tropical Medicine Research Institute, University of West Indies	West Indies
Dr Nassirou GERALDO	Physician / epidemiologist, Projet SIDA-2, Benin	Benin
Dr Roger GLASS	Center for Disease Control and Prevention	US
Rev. Rupert HAMBIRA	Senior Education Community Advisor, 'Maiteko a Tshireletso' Vaccine Initiative Botswana-Harvard Partnership for HIV Research and Education, Gaborone	Botswana
Dr IDÄNPÄÄN-HEIKKILÄ	Secretary-General, CIOMS	Switzerland
Professor Sir Bob HEPPLE	Chairman, Nuffield Council on Bioethics	UK
Professor Mariana KRUGER	Faculty of Health Sciences, University of Pretoria, SA MRC Ethics Committee	South Africa
Professor Dominic KWIATKOWSKI	Oxford University	UK
Dr Richard LANE	Director of Science, Natural History Museum, Former Head of International Programmes, The Wellcome Trust.	UK
Mr Tim MARTINEAU	Senior Health Advisor, Department for International Development (DFID)	UK
Professor Keith McADAM	London School of Hygiene and Tropical Medicine	UK
Dr Mahdi RAMSAN MOHAMED	Deputy Director, Public Health Laboratory-Ivo de Carneri Ministry of Health, Zanzibar	Tanzania
Professor Malcolm MOLYNEUX	Head, Wellcome Trust Unit	Malawi

Continued

Name	Organisation*	Country
Dr Keymanthri MOODLEY	Tygerberg Division Centre for Applied Ethics & Faculty of Health Sciences, University of Stellenbosch	South Africa
Mrs Doreen MUKWAMATABA	Nursing Services Manager, Tropical Diseases Research Centre	Zambia
Professor Kim MULHOLLAND	Centre for International Child Health	Australia
Dr Alwyn MWINGA (unable to attend)	Medical epidemiologist, CDC Global AIDS Program (GAP), Lusaka	*Zambia*
Dr Chaichana NIMNAUN	Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok	Thailand
Mr Bernhards OGUTU	Centre for Clinical Research, Kenya Medical Research Institute	Kenya
Prof Hennnie OOSTHUIZEN	SA MRC Ethics Committee	South Africa
Ms Delia OUTOMURO	Faculty of Medicine, University of Buenos Aires	Argentina
Professor Catherine PECKHAM	Head, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health. Member, Nuffield Council on Bioethics	UK
Dr Raul PEREA-HENZE	Worldwide Science Policy, Pfizer, Inc.	US
Nicola PERRIN	Public Liaison Officer, Nuffield Council on Bioethics	UK
Professor William PICK	Acting President, SA MRC	South Africa
Professor Marie POGGENPOEL	SA MRC Ethics Committee	South Africa
Mr Hadi PRATOMO	Faculty of Public Health, The University of Indonesia	Indonesia
Dr Jan PRYOR	Fiji School of Medicine, Fiji Islands	Fiji
Dr Asad RAJA	Department of Surgery, Aga Khan University Hospital, Nairobi	Kenya
Mr Edwin RAMIREZ	Dos de Mayo National Hospital, Lima	Peru
Professor Harun-Ar-RASHID	Director, Bangladesh Medical Research Council, Dhaka	Bangladesh
Professor Priscilla REDDY (unable to attend)	Director of Health Promotion Research and development, SA MRC	South Africa

Continued

Name	Organisation*	Country
Dr Charles ROTIMI	National Human Genome Center	US
Mr Harald SCHMIDT	Assistant Director, Nuffield Council on Bioethics	UK
Dr Lizette SCHOEMAN	University of Pretoria	South Africa
Mr François SIMONDON	Head, Epidemiology and Research Unit, IRD Montpellier	France
Ms Catherine SLACK	HIV AIDS Vaccines Ethics Group (HAVEG), School of Psychology, University of Natal	South Africa
Professor Peter SMITH	Professor of Tropical Epidemiology, London School of Hygiene & Tropical Medicine. Member, Nuffield Council on Bioethics	UK
Dr Bella STARLING (unable to attend)	Programme Officer, History of Medicine and Biomedical Ethics, The Wellcome Trust	UK
Dr Athula SUMATHIPALA	Director, Bioethics initiative, Forum for Research and Development	Sri Lanka
Dr Sandy THOMAS	Director, Nuffield Council on Bioethics	UK
Dr Nadia TORNIEPORTH	Vice President, Clinical Development, Prophylactic Vaccines, GlaxoSmithKline Biologicals	Belgium
Dr Cristina TORRES	Treasurer, FLACEIS	Mexico
Dr. Yupaporn WATTANAGOON	Initiative for Vaccine Research (IVR) Unit, World Health Organization	Switzerland
Professor Jimmy WHITWORTH	Professor of International Public Health, Infectious Diseases Epidemiology Unit, London School of Hygiene and Tropical Medicine, London	UK
Mr Zhiyong ZONG	Department of Infectious Diseases, West China Hospital, Sichuan University	China

* Positions at time of Workshop, February 2004.

Appendix D: Background literature

- SciDev.net: Dossier on ethics of research
  www.scidev.net

- Glasa J (ed.) (2001) *Ethics committees in Central and Eastern Europe* (Council of Europe IMEB Foundation and Charis).

- Huriet C, Riis P *et al*. (2004) *Ethical Eye: Biomedical Research* (Council of Europe).

- Macklin R (2004) *Double Standards in Medical Research in Developing Countries* (Cambridge University Press).

- Riis P (1998) *Ethical Review of Biomedical Research in Europe: Suggestions for best national practices* (Council of Europe).

- Ziemele I (ed.) (2002) The Baltic Yearbook of International Law Volume 2, Special Theme *Biomedicine and human rights*.

Glossary

Acquired Immune Deficiency Syndrome (AIDS): A disease caused by retroviral infection with the human immunodeficiency virus (HIV-1, HIV-2). The disease leads to failure of the immune system and debilitation, and is often accompanied by infections such as tuberculosis. The disease is transmitted through direct contact with bodily fluids (e.g. blood-blood or via sexual intercourse).

Aetiology: Study of the causes or origins of a disease or abnormal condition.

Antigen: A foreign molecule that triggers an antibody response.

Anti-retroviral therapy: A group of medicines used in the treatment of HIV/AIDS.

Cerebrospinal meningitis: Cerebrospinal meningitis or meningococcal meningitis is a contagious disease caused by the bacteria *meningococcus*. It causes both sporadic and **epidemic** outbreaks, predominantly in children and young adults. The disease is characterised by inflammation of the meninges (three layers of connective tissue that envelop the brain and spinal cord); the symptoms include severe headache, photophobia (light sensitivity) and neck stiffness. The disease can be severe with high mortality rates, or result in permanent neurological disability.

Clinical research and clinical trials: Medical research studies designed to answer scientific questions and to find better ways to prevent, detect, or treat disease. A large number of clinical trials are confined to testing the safety and efficacy of new medicines. There are generally four separate phases of such trials:

- ***Phase I trials:*** Phase I studies will be the first time human subjects are exposed to the potential new medicine. The objectives of the study will be to investigate pharmacodynamics, dose-response, and in the case of vaccines, immune response, and to determine the maximum dose that can be tolerated by participants. In the case of most new medicines these studies will be undertaken in a small number of healthy volunteers. Evidence for the efficacy of the medicine would not normally be provided by Phase I studies.
- ***Phase II trials:*** Using the information about the safe dosage range obtained from the Phase I studies, the compound will be administered to patients suffering from the target disease. Significant numbers of individuals will be recruited into the trial at a number of clinical centres. The objective of the Phase II studies will be to seek evidence of the efficacy of the medicine against the specific disease. More information about the safety of the medication will emerge from these studies as larger numbers of individuals are exposed to the medicine. In Phase II trials, the patient will often be randomly assigned to the novel treatment group or to a group receiving a placebo (a compound possessing no therapeutic effect) or, more usually, a conventional and established treatment.
- ***Phase III trials:*** Where a compound has shown evidence of efficacy without significant side effects, it will enter Phase III trials. Many hundreds, or sometimes a few thousand patients will be enrolled. These trials will generally seek not only to confirm the clinical efficacy of the novel compound, but also to establish its efficacy in comparison to existing treatments. These studies will often be multicentre and sometimes undertaken on an international basis. Again, careful attention is paid to possible side effects as larger numbers of patients are exposed to the intervention. The end-points for Phase III studies include the demonstration of a statistically significant improvement in the efficacy of the novel medicine over the established therapies, if any such exist.
- ***Phase IV trials:*** Once a new medicine reaches the market it will be subjected to post-marketing surveillance in order to identify side-effects and other adverse effects which would only become evident as much larger numbers of individuals are treated. In addition,

formal clinical trials continue in order to develop a greater understanding of the compound and its effects in a wider clinical environment. Further study may also extend its use for other indications or for different patient groups, such as children or the elderly. Special study designs may be used according to the objectives of the study to evaluate safety or efficacy. These may include study of temporal trends, case-control studies, or the phased introduction of an intervention in different areas. Phase IV studies may also be designed to measure the impact of the intervention on the **epidemiological** pattern or the transmission of an **infectious disease**.

Conjugate: Paired together, such as in pneumococcal conjugate vaccines for pneumonia and meningitis.

Control: A control group in **clinical research and clinical trials** contains participants who are not given the intervention which is being tested in the research. The results of the control group will be compared with a group who are given the intervention. In clinical trials, the intervention would normally be a novel treatment, such as a medicine or vaccine. Interventions may also be social and behavioural in nature, such as, safe sex campaigns.

Epidemic: A temporary increase in the prevalence of a disease within a specific community or region. The rise in prevalence may last a few weeks or years.

Epidemiological research: Research concerned with describing and explaining the occurrence of disease in populations.

Haplotype: A specific combination of linked alleles in a cluster of related genes. An allele is a variant form of a gene, which differs in DNA sequence from alternative alleles of the same gene.

HapMap: An international project established in 2002 to create a haplotype map of the human genome. The project will describe the common patterns of human DNA sequence variation and may be used to identify genes linked to susceptibilities to disease. Researchers from Canada, China, Japan, Nigeria, the UK and US expect to complete the map by 2005.

Hepatitis B: A virus transmitted through body fluids by poor surgical sterilisation procedures, close contact, blood contamination, infection at birth, needle sharing or sexual contact. It causes an acute illness, which may develop into chronic hepatitis. Symptoms include tiredness, sickness, fever, loss of appetite, stomach pains, and diarrhoea. Symptoms may also include dark yellow urine, and yellowish eyes and skin (also called jaundice).

Hib disease: Hib disease is a group of diseases caused by the *Haemophilus influenzae* type B bacteria e.g. pneumonia and bacterial meningitis.

Hib polysaccharide – protein conjugate vaccine: A vaccine for Haemophilus influenzae type B containing a 'weak' polysaccharide (complex naturally occurring carbohydrates e.g. starch) linked to a protein.

Hypertension: Persistently high arterial blood pressure, which may have no known cause or be associated with other diseases. Hypertension is a risk factor for the development of diseases such as heart disease and stroke.

Infectious diseases: Infectious or communicable diseases are caused by living organisms, mainly micro-organisms (e.g. viruses, bacteria and fungi and groups intermediate between viruses and bacteria e.g. chlamydiae). The source of disease can be another human, animal or insect. Transmission occurs via several routes (e.g. physical contact, food and drink) and organisms typically enter the body by inhalation or direct contact.

Ivermectin: One of a class of medicines used to treat infestation with several species of nematode worms transmitted by biting insects. It is used as the medicine of choice for the treatment of **onchocerciasis**.

Morbidity: Levels of sickness and ill health.

Non-communicable diseases: Diseases caused by factors other than living organisms, such as lifestyle, diet, genes or a combination of factors. Examples of non-communicable diseases include mental disorders, heart disease, and cancer.

Non-infectious diseases: See *non-communicable diseases*.

Onchocerciasis ('River Blindness'): Onchocerciasis is a parasitic disease transmitted by simulium flies, which breed in fast-flowing rivers and streams. The parasites migrate to different parts of the human body, including to the eyes where they may cause blindness.

Perinatal transmission: Transmission of an infection-causing agent, such as HIV, from mother to child in the period either shortly before or after birth.

Primary endpoint (of a clinical trial): The principal result that is measured at the end of a study to establish whether a given treatment was effective.

Prophylactic: Preventive measure, including medication.

Randomised controlled trials: An experiment in which investigators randomly allocate eligible participants into **control** and intervention groups to receive one or more interventions that are being tested. The results are assessed by comparing outcomes of the two groups.

Rectal artesunate: An anti-malarial medicine administered as a suppository.

Rotavirus vaccines: Vaccines for immunisation against rotavirus, the commonest cause of severe diarrhoea among children worldwide.

Serotype: A group of closely related microorganisms (including bacteria, viruses, fungi and protozoa) distinguished by a characteristic set of **antigens**.

Glossary of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Treatment/Therapy
CAB	Community Advisory Board
CDBI	Steering Committee on Bioethics of the Council of Europe
CIOMS	Council for International Organizations of Medical Sciences
CoE	Council of Europe
CONEP	National Ethics in Research Committee (Brazil)
DEC	Diethylcarbamazine
DNA	Deoxyribonucleic acid
DTP-Hib	Combination vaccine: diphtheria, tetanus, pertussis and *Haemophilus influenzae* type B
EGE	European Group on Ethics in Science and New Technologies
EU	European Union
FDA	United States Food and Drug Administration
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
ITNs	Insecticide-treated nets
KAVI	Kenya AIDS Vaccine Initiative
MDG	Millennium Development Goals
MRC	Medical Research Council
NBAC	National Bioethics Advisory Commission (US)
NCD	Non-Communicable Disease
NCOB	Nuffield Council on Bioethics (UK)
NIH	National Institutes of Health (US)
PABIN	Pan-African Bioethics Initiative
RECs	Research Ethics Committees
SA MRC	Medical Research Council of South Africa
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organization
WMA	World Medical Association

Index

Genetic screening: ethical issues
Published December 1993

Human tissue: ethical and legal issues
Published April 1995

Animal-to-human transplants: the ethics of xenotransplantation
Published March 1996

Mental disorders and genetics: the ethical context
Published September 1998

Genetically modified crops: the ethical and social issues
Published May 1999

The ethics of clinical research in developing countries: a discussion paper
Published October 1999

Stem cell therapy: the ethical issues – a discussion paper
Published April 2000

The ethics of research related to healthcare in developing countries
Published April 2002

The ethics of patenting DNA: a discussion paper
Published July 2002

Genetics and human behaviour: the ethical context
Published October 2002

Pharmacogenetics: ethical issues
Published September 2003

The use of genetically modified crops in developing countries: a follow-up Discussion Paper
Published December 2003

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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 Subjects*. Geneva 1993.

Council for International Organizations of Medical Sciences (CIOMS). I*nternational Guidelines for Ethical Review of Epidemiological Studies*. Geneva 1991.

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 Biomedicine*. European Treaty Series – No. 164. Oviedo, 4 April 1997.

Department of Health, Education, and Welfare, Office of the Secretary, Protection of Human Subjects. *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Report of the National Committee for the Protection of Human Subjects of Biomedical and Behavioural Research*. DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014. 18 April 1979.

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) 1 May 1996.

World Health Organization (WHO). Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. Annex 3 of *The Use of Essential Drugs*. 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 Subjects*. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical 23.Assembly, Venice, Italy, October 1983; the 41st World Medical Assembly, Hong Kong, September 1989; and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

World Medical Association, *Declaration of Lisbon on the Rights of the Patient*. Adopted by the 34th World Medical Assembly, Lisbon, Portugal, September/October 1981 and amended by the 47th General Assembly, Bali, Indonesia, September 1995.

Operational Guidelines for
Ethics Committees Reviewing
Biomedical Research
UNDP/World Bank/WHO Special Program for Research & Training in Tropical Diseases
(TDR)

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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 Harmonisation, 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:

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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
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

THE BELMONT REPORT
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

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfillingthis part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy.

NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

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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.

PART A: BOUNDARIES BETWEEN PRACTICE & RESEARCH

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 undergoreview 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 the terms "experimental" and "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.

PART B: BASIC ETHICAL PRINCIPLES

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.

PART C: APPLICATIONS

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 an 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 determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Useful Internet Sites for Researchers and Ethics Committee Members

Council for International Organizations of Medical Sciences (CIOMS)
http://www.cioms.ch/

European Network for Biomedical Ethics
http://www.izew.uni-tuebingen.de/bme/

International Conference on Harmonization (ICH), Guidelines for Good Clinical Practice
http://www.ich.org/LOB/media/MEDIA482.pdf

Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries*
http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction

Nuremberg Code
http://ohsr.od.nih.gov/guidelines/nuremberg.html

Program on Ethical Issues in International Health Research, Harvard School of Public Health
http://www.hsph.harvard.edu/bioethics/

UNESCO, Global Ethics Observatory, Division of Ethics of Science and Technology
http://portal.unesco.org/shs/en/ev.php-URL_ID=6200&URL_DO=DO_TOPIC&URL_SECTION=201.html

United Nations, Universal Declaration of Human Rights
http://www.un.org/Overview/rights.html

U.S. Agency for International Development, *Guide for Interpreting the Federal Policy for the Protection of Human Subjects*
http://www.usaid.gov/our_work/global_health/home/TechAreas/commrule.html

U.S. Centers for Disease Control and Prevention, Epidemiology Program Office, Office of the Associate Director for Science
http://www.cdc.gov/od/science/regs/hrpp/training.htm

U.S. Department of Health and Human Services, Office for Human Research Protections
http://www.hhs.gov/ohrp/ http://www.hhs.gov/ohrp/international/HSPCompilation.pdf

U.S. Department of Health and Human Services, Office of Research Integrity
http://ori.dhhs.gov/

U.S. Food and Drug Administration, Information Sheets, *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors*
http://www.fda.gov/oc/ohrt/irbs/default.htm

U.S. National Institutes of Health, *Bioethics Resources on the Web*
http://bioethics.od.nih.gov/

U.S. National Institutes of Health, Office of Extramural Research, *Protecting Human Research Participants*
http://phrp.nihtraining.com/users/login.php

U.S. President's Council on Bioethics
http://bioethics.gov/

University of Minnesota, *Web-Based Instruction on Informed Consent*
http://www.research.umn.edu/consent/orientation.html

World Health Organization
http://www.who.int/en/

World Medical Association
http://www.wma.net/e/

Selected Bibliography

Angell M. The ethics of clinical research in the third world. *N Engl J Med* 1997;337:847-49.

Cox LE, Rouff JR, Svendsen KH, et al. Community advisory boards: their role in AIDS clinical trials. *Health Soc Work* 1998;23(4):290-97.

Emanuel EJ, Wendler D, Killen J, et al. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis* 2004;189(5):930-37.

Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292(13):1593-1601.

Koski G. Risk, benefits, and conflicts of interest in human research: ethical evolution in the changing world of science. *J Law Ethics* 2000;28:300-31.

Lo B, Bayer R. Establishing ethical trials for treatment and prevention of AIDS in developing countries. *BMJ* 2003;327(7410):337-39.

MacQueen KM, Karim QA, Sugarman J. Ethics guidance for HIV prevention trials. *BMJ* 2003;327(7410):340.

MacQueen KM, McLellan E, Metzger DS, et al. What is community? An evidence-based definition for participatory public health. *Am J Pub Health* 2001;91(12):1929-38.

Macklin R. Understanding informed consent. *Acta Oncológica* 1999;38:83-87.

Mariner WK, McArdle PA. Consent forms, readability, and comprehension: the need for new assessment tools. *Law Med Health Care* 1985;13(2)68-74.

Quinn SC. Ethics in public health research: protecting human subjects: the role of community advisory boards. *Am J Pub Health* 2004;94(6):918-22.

Rivera R, Borasky D, Rice R, et al. Informed consent: an international researchers' perspective. *Am J Pub Health* 2007;97(1):25-30.

Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? *PLoS Med* 2005;2(9):824-27.

Sullivan M, Kone A, Senturia KD, et al. Researcher and researched—community perspectives: toward bridging the gap. *Health Educ Behav* 2001;28(2):130-49.

U.S. Department of Health and Human Services. *Creating Partnerships, Improving Health: The Role of Community Based Participatory Research.* Washington, DC: U.S. Department of Health and Human Services, Agency for Healthcare Research Quality, 2003.

Weijer C, Emanuel EJ. Ethics. Protecting communities in biomedical research. *Science* 2000;289(5482):1142-44.

World Health Organization. *Indigenous Peoples and Participatory Health Research.* Geneva: World Health Organization, Centre for Indigenous Peoples' Nutrition and Environment, 2003.

Basic Research Ethics Documents

The Belmont Report
http://ohsr.od.nih.gov/guidelines/belmont.html

Declaration of Helsinki, World Medical Association, 2008
http://www.wma.net/en/30publications/10policies/b3/index.html

International Ethics Guidelines for Biomedical Research Involving Human Subjects, CIOMS, 2002
http://www.cioms.ch/frame_guidelines_nov_2002.htm

Operational Guidelines for Ethics Committees That Review Biomedical Research, World Health Organization, 2000
http://www.who.int/tdr/publications/publications/ethics.htm

U.S. Code of Federal Regulations, Title 45, Part 46
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm