

Operating Guidelines for the Protection of Human Subjects Committee

Table of Contents

Introduction	Page 1
Purpose and Charge to the Committee	Page 1
Composition of the Committee	Page 1
Responsibilities and Duties of the Committee	Page 2
Methods of Operation	Page 2
Appendix I	Declaration of Helsinki
Appendix II	Committee Roster and Brief Biodata Profiles
Appendix III	Policies for Protection of Human Subjects Committee
Appendix IV	Protection of Human Subjects Committee Forms
Appendix V	Declaration by Member of FHI Protection of Human Subjects Committee Regarding Conflicts of Interest
Appendix VI	Informed Consent Procedures
Appendix VII	Definition of Terms

1

Introduction

Family Health International (formerly International Fertility Research Program-IFRP) is a not-for-profit institution engaged in the clinical evaluation of the safety and effectiveness of experimental contraceptive products, AIDS (Acquired Immune Deficiency Syndrome) and STDs (sexually transmitted diseases) prevention (health intervention, technical and medical assistance primarily to governments of developing countries); and studies involving reproductive health, epidemiology research, and maternal/child health. Attention is devoted to training programs for improving health provider family planning service delivery in developing countries. Under its institutional development program, FHI provides funding and technical support to Family Health Research Centers (FHRCs) in a number of developing countries to enable them to respond to their own family planning and reproductive health needs. Founded as IFRP in July 1971, the institution is governed by an international Board of Directors (listed below) that reviews FHI program activities and goals and provides policy direction. The institution is funded by US Federal sources, international agencies, philanthropic institutions, private sources and, in selected cases, implements contracts with pharmaceutical manufacturers. In performing its research activities, FHI complies with the Helsinki Declaration, as amended (Appendix I), and all applicable US Federal regulations.

I. Purpose and Charge to the Committee

The Protection of Human Subjects Committee (PHSC) for FHI was established in March 1975. (Prior to 1975, the Committee on the Protection of the Rights of Human Subjects of the School of Medicine of the University of North Carolina, Chapel Hill, served as this committee.) The Committee may act as the ethical review board for other institutions upon request. The purpose of the Committee is to protect human subjects through the review of proposals for research to be conducted by FHI and other institutions served by the Committee. The Committee also reviews the procedures for recruitment of subjects into studies to assure that the process is equitable and free of coercion. The Committee functions as an Institutional Review Board (IRB) for FHI and other institutions in accordance with the Code of Federal Regulations, 45 CFR 46, 21 CFR 812 and 21 CFR 50 and 56. Each Committee member receives the current version of these regulations. Committee members periodically receive updated information from attendance at workshops and seminars such as those sponsored by the National Institutes of Health and the US/Food and Drug Administration.

These Operating Guidelines were developed to comply with the HHS/NIH/PHS Federal Regulations (45 CFR 46) (including the common Federal Rule, effective 8/19/91) and FDA Federal Regulations (21 CFR 812 and 21 CFR 50 and 56). In the event of a conflict between them, the regulations shall govern. In the event the Operating Guidelines omit substantive material, the regulations are incorporated by reference.

II. Composition of the Committee

The Committee is composed of a minimum of five and a maximum of ten members sufficiently qualified to execute the Committee's charge. All members are appointed by the President/Chief Operating Officer of FHI. The Committee is composed primarily of scientific and non-scientific men and women of diverse cultures and disciplines from the Chapel Hill, Durham and Raleigh area. One non-voting member of the Committee is a full-time employee of FHI. Each institution for whom the Committee serves as an Institutional Review Board also nominates a non-voting

1-

2

Family Health International Board of Directors

Torrey C. Brown, (Chair)
Secretary
Department of Natural Resources
State of Maryland
Annapolis, MD

Pramilla Senanayake, (Vice Chair)
Assistant Secretary-General
International Planned Parenthood Federation
London, United Kingdom

David W. Barry
Vice President
Research Development & Medical Affairs
The Wellcome Research Laboratories
Burroughs Wellcome Co.
Research Triangle Park, NC

Arthur C. Christakos
Professor (Retired)
Obstetrics-Gynecology
Duke University Medical Center
Durham, NC

Donald A. Collins
President
International Services Assistance Fund
San Francisco, CA

John L. Ganley
Consultant
Georgetown, SC

Wilbur James Gould
Founder-Director
Ames Vocal Dynamics Laboratory
New York, NY

Theodore M. King
President/Chief Operating Officer
Family Health International
Durham, NC

Luella V. Klein
Professor
Department of Gynecology/Obstetrics
Emory University School of Medicine
Atlanta, GA

Ursula Lachnit-Fixson
Obstetrics/Gynecology Specialist
Schering Research Foundation, Ltd.
Berlin, Germany

Nancy Ostrander
US Ambassador (Retired)
Indianapolis, IN

Donald R. Seawell
Chairman of the Board
The Denver Center for the Performing Arts
Denver, CO

Roger V. Short
Professor
Department of Physiology
Monash University
Clayton, Victoria, Australia

R. Peyton Woodson, III
Former Chairman of the Board
British-American Insurance Company, Ltd.
Raleigh, NC

Harry Woolf
Institute for Advanced Study
Princeton, NJ

member to the Committee. This member, who is an officer or employee of the nominating institution, is only present and participates during the Committee's consideration of studies from his or her institution. The current membership of the Committee and the classification of each member are cited in Appendix II. The selection criteria and the composition of the Committee are contained in a statement of policy in Appendix III.

III. Responsibilities and Duties of the Committee

The Committee meets at least three times during the year and reviews research proposals that involve human subjects. All continuing research projects are reviewed at least annually or more frequently at intervals relative to the degree of risk as determined by the Committee. Decisions are based upon the majority vote of the members present at a meeting. The presence of a simple majority of voting members (one more than 50% of the voting membership) is necessary to constitute a quorum. A member with a conflicting interest shall be counted present for purposes of calculating a quorum. At least one non-scientific member must be present for the review of proposals. The Chairperson of the Committee is responsible for chairing the meetings, conducting the business so that each proposal is thoroughly reviewed and seeing that the Committee makes a decision about the disposition of each proposal. Minutes of the meetings are recorded by the Secretary to the Committee, and subsequently signed by the Chairperson following Committee review and approval. The Secretary is also responsible for maintaining the rosters and curricula vitae of the Committee, minute records, research proposals and documentation of the Committee's decisions (including continuing review activities), and written procedures for the Committee.

The Committee may function as a non-local Institutional Review Board for investigators who are unaffiliated with an established local Institutional Review Board.

IV. Methods of Operation of the Committee

1. Criteria for Exemption, Expedited and Committee Review

- a. In accordance with 45 CFR 46.101(b), certain research activities involving human subjects are **exempt** from the Federal Regulations, and, therefore, the Committee's review unless the research is covered by other subparts of Part 46:
 - (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 45 CFR 46.101, 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 Federal 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.
- b. The Committee may delegate to its Chairperson the right to grant selected interim administrative approvals. The Chairperson or the Vice Chairperson may perform the review of research activities with human subjects involving no more than minimal risk through the **expedited review** procedure as stipulated in 21 CFR 56.110 and as cited at 46 Federal Register 8960 (January 27, 1981). The categories of research activities which may be reviewed via the **expedited review** procedure are subject to regulatory amendment. These presently include:
- (1) Collection of: hair and nail clippings, in a non-disfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.
 - (2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
 - (3) Recording of data from subjects 18 years of age or older using non-invasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subjects privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography,

electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

- (4) Collection of blood samples by venipuncture, in amounts not exceeding (450 milliliters in an eight-week period and no more often than two times per week from subjects 18 years of age or older who are in good health and not pregnant.
- (5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
- (6) Voice recordings made for research purposes such as investigations of speech defects.
- (7) Moderate exercise by healthy volunteers.
- (8) The study of existing data, documents, records and pathological specimens or diagnostic specimens.
- (9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate the subjects' behavior and the research will not involve stress to subjects.
- (10) Research on drugs or devices for which an IND (Investigational New Drug) exemption or IDE (Investigational Device Exemption) is not required.
- (11) Other categories designated at the regulatory level and published in the Federal Register.

The Committee may also use the **expedited review** process to review minor changes in previously approved research during the period for which approval is authorized. All research activities approved by the Chairperson or the Vice Chairperson (in the absence of the Chair) via the expedited review procedure must be subsequently ratified by the Committee. If the Chairperson or the Vice Chairperson is unwilling to approve an expedited review request, the proposal shall be submitted to the Committee for review.

- c. **Proposals not meeting the criteria for exemption or expedited review must undergo Committee review.**
- d. Documentation of criteria for Committee review of proposal summaries are found in Appendix III. Proposed research studies are submitted to the Committee for review and consideration of approval. Complete protocols for initial proposals are accompanied by a Proposal Summary (Appendix IV). Data collection forms are provided to the Committee on request.

- e. An amended protocol is accompanied by a Proposal Summary, which describes the deviations from the initially PHSC-approved submission. When an amended proposal differs substantially in study design or procedures from a previously approved study, the initial protocol will accompany the amended proposal submission.

2. Children as Research Subjects

- a. Children are permitted to be research subjects under the following conditions:
 - (1) The research does not involve greater than minimal risk.
 - (2) There is greater than minimal risk; however, there is reasonable likelihood the intervention or procedure will be of direct benefit to the individual subject or by a monitoring procedure that it is likely to contribute to the subject's well-being, only if the Committee finds that:
 - (a) the risk is justified by the anticipated benefit to the subjects; and
 - (b) the relationship of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.
 - (3) The intervention or procedure involves greater than minimal risk without the prospect of direct benefit to the individual subjects, or is a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the Committee 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; and
 - (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.
- b. In all cases, the Committee shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the Committee the children are capable of providing assent. "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. Also the Committee shall determine that adequate provisions are made for soliciting the permission of each child's parents or guardians. Further information on assent and permission is found in 45 CFR 46.408.
- c. The additional protections for children involved as subjects in research (45 CFR 46, Subpart D) shall be employed as defined in the regulations.

3. Informed Consent

- a. Each proposal submission will include a consent form or detailed reasons for the exclusion of a consent form (Appendix VI). A Checklist of the Essential Elements of Informed Consent and Model Informed Consent Document are found in Appendix VI. Simple and understandable consent form language is emphasized by the Federal regulations and the Committee. To facilitate comprehensible and readable consent forms, the Committee has adopted:
 - (1) a reading score of 6th grade level or less for developing countries and up to grade 8 for developed countries, using the Fry Graph for the English language, and the adaptation of measures to increase the accuracy of the readability grade level determination as cited in Appendix VI, in the section on *Recommendations from Seminar on Readability and Comprehensibility of Text*;
 - (2) use of the Crawford Graph for Spanish informed consent documents, and;
 - (3) application of the principles of writing "friendly" text. (See Appendix VI, in the section on *Writing "Friendly" Text* by Alan N. Crawford.)

When consent forms are translated into foreign languages, a statement will be furnished to the Committee attesting to the accuracy of the translation.

4. The Review Process

- a. Submissions to the Committee are transmitted by the Secretary to the Committee at least ten days in advance of each meeting. Committee members receive all necessary supporting information for each proposal to ensure complete and adequate review. The Committee Chairperson shall select at least two primary reviewers (one scientific/one non-scientific) for each proposal.
- b. At each Committee meeting, appropriate management staff are available to answer questions and to provide additional information on the submitted proposals.
- c. At each Committee meeting, each proposal will be presented in sufficient detail by one of the primary reviewers to permit adequate consideration. Following this presentation, the proposal will be discussed by all members until a decision is reached.
- d. The Committee by majority vote of those present may reach one of the following decisions regarding each proposal: a) Approval as presented, b) Approval subject to modifications, c) Disapproval, d) Deferral or e) No action, pending evaluation of additional information requested.
- e. Any Committee member who has a conflicting interest in a proposal will abstain from the Committee's deliberations on the proposal, except to provide information if requested by the Committee. A member who has such a conflict of interest may not vote on the proposal. Appendix V contains the "Declaration by Member of FHI Protection of Human Subjects Committee Regarding Conflicts of Interest," which is submitted at least annually by Committee members.

- f. If the Committee approves a proposal subject to modifications, then the Committee will decide by majority vote of those present if required changes to the proposal require full Committee review or may be approved by the Chairperson on behalf of the full Committee.
- g. When a proposal is approved, FHI or other responsible institutions and the investigator(s) will be informed of the specific duration of this approval (one year maximum). In addition, the frequency of review will be designated by the Committee and documented in the minute record. Continuing review frequency other than on an annual basis will also be documented in the PHSC Index of Ongoing Proposals. Disapproved proposals may be resubmitted to the Committee for reconsideration.
- h. The decisions of the Committee will be included in the file records of the proposals maintained by the Secretary.
- i. Requests for continuation and re-evaluation; the cancellation or completion of a research project will be submitted to the Committee.
- j. In circumstances of collaborative studies, the review of another Institutional Review Board may be accepted, but only if a favorable review is satisfactorily documented and if such review is acceptable to the Committee.
- k. The Committee may at any time request a review and/or opinion by a qualified expert outside the Committee when specialized review is necessary.

5. Committee Records

- a. A summary of the Committee's discussions and a recording of the decisions, which shall include but not be limited to the final disposition of each proposal, shall be made by the Secretary to the Committee. The minute record will be submitted to the Committee for review and approval. On approval, the minute record will be executed by the Chairperson, on behalf of the Committee.
- b. FHI and other institutions served by the Committee receive the minutes and a summary of each meeting. Investigators are formally notified of the Committee's approval of a proposal and whenever an activated proposal must be cancelled and the reasons thereof.
- c. The Secretary to the Committee shall maintain a permanent file of records of each proposal submitted. These records shall include:
 - (1) The original research proposal, the Committee's amendments, and certification by the Chairperson of the Committee;
 - (2) The records of periodic re-evaluation.

The Secretary shall also keep files of the Operating Guidelines for the Committee, minutes of the meetings, and communications with the Committee members.

- d. The PHSC files will be continually available for review by authorized persons including representatives of the State or Federal government, FHI staff, and sponsors of the

research activities. The PHSC records related to research proposals shall be retained for at least three years after the research is completed or cancelled.

6. Institutional Representatives

- a. The non-voting institutional representatives on the Committee shall be primarily concerned with the protection of human subjects. These representatives shall provide direct communication between the Committee and investigators for whom the Committee is serving as an institutional review board. In addition, these representatives shall coordinate submission of the following:
 - (1) safety data reports,
 - (2) adverse experience reports,
 - (3) study status reports from investigators using the Committee as their institutional review board, and
 - (4) notification to each investigator for whom the committee serves as an institutional review board of the Committee's review and decisions of research protocols and any subsequent amendments.
- b. If the Committee is acting as an ethical review board for another institution, that institution shall also appoint a non-voting institutional representative. All institutional representatives have primary responsibility for the reports and communications listed above, and maintaining files and records relating thereto.

7. Reporting Requirements

- a. The institutional representative coordinates the submission of **safety data reports** submitted annually (or as designated) to the Committee, which summarize the Serious Adverse Experiences for each ongoing study. Serious is defined as:
 - (1) fatal or immediately life-threatening,
 - (2) hazard to life, contraindication, side effect or precaution;
 - (3) permanently disabling,
 - (4) required inpatient hospitalization,
 - (5) congenital anomaly,
 - (6) cancer, or
 - (7) overdose.

These reports show the frequency of serious adverse experiences by investigator, investigational product and study site. These reports shall be furnished to the Committee as part of the continuing review process until the study is either cancelled or completed.

- b. The Committee shall be informed as soon as the institutional representative receives the **adverse experience report** (Appendix IV) of all Serious Adverse Experiences (SAEs) that are judged by staff medical reviewers to be:

- (1) fatal,
- (2) life-threatening or
- (3) serious, related to the study product and unexpected.

Unexpected is defined as: not identified in nature, severity, or frequency in the current study protocol and/or investigator brochure (if applicable). Reports which show the relative frequency of serious adverse experiences for the study in which the event occurred will be provided at the next Committee meeting following the notification. This report will assist in the determination of the event's possible significance as a warning of undue risks to human subjects. Any additional concerns or requests for further information from the Committee in regard to adverse experiences will be handled by the non-voting institutional representatives.

- c. The Committee shall be informed of any problems in a study that may place subjects or others at an increased risk, and of any changes to a study which may be material to the Committee's duties. FHI and the other institutions served by the Committee agree to report to the Committee any serious or continuing noncompliance by investigators with the Committee's requirements or applicable Federal regulations.
- d. The Chairperson of the Committee shall have the right to suspend temporarily any research activities when untoward or unexpected adverse events occur. In the event this occurs, the proposal will be re-evaluated and a decision reached by the full Committee at its next meeting. The Committee may suspend or stop research not conducted according to its requirements or associated with unexpected, serious harm to its subjects (45 CFR 46.113).
- e. The institutional representatives will coordinate the submission of study status reports (Appendix IV) from investigators using the Committee as their institutional review board.
- f. The Committee shall report any noncompliance with its requirements as may be required by applicable Federal regulations.

8. Family Health Research Centers

- a. Research activities carried out by Family Health Research Centers (FHRCs) fall into four categories:
 - (1) Research conducted under contract with FHI. Such research uses standard FHI protocols, data collection instruments and informed consent procedures, and is reviewed by the Committee through its regular review of FHI research proposals.
 - (2) Research of a programmatic nature (ie, research that is of local interest, but not part of an FHI research strategy) funded by FHI. Such research uses US/FDA-approved drugs or devices, or drugs or devices approved for use in the host

country, and FHI protocols, data collection instruments and informed consent procedures that have been reviewed and approved by the Committee. The Committee will be informed of such studies planned and in progress within the FHRCs.

- (3) Research of a programmatic nature, funded by FHI, for which FHI has not been responsible for development of the protocol or data collection forms. In these cases a project design summary is developed and reviewed by FHI as well as by local research review boards prior to study initiation. Information on these studies will be furnished to the Committee.
- (4) Research conducted by the FHRC with non-FHI funding. Research of this type will not be submitted to FHI's Committee for review and approval.

Each FHRC has its own research review committee that includes responsibility for ethical issues and protection of human subjects in accordance with local requirements. Thus, all research conducted by the FHRC, regardless of funding source, is regularly reviewed for the protection of human subjects on a local basis.

March 5, 1993

Appendices

Appendix I

Declaration of Helsinki

DECLARATION OF HELSINKI

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol and transmitted to the independent committee (1, 2).
6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that the medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Nontherapeutic Biomedical Research Involving Human Subjects (Nonclinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1961, and revised by the 41st World Medical Assembly, Hong Kong, 1989.

15

Appendix II

Committee Roster and Brief Biodata Profiles

Family Health International

Protection of Human Subjects Committee

1993 Roster

Clergy

- 1993 Dennis M. Campbell, PhD, BD (*Chair*)
Dean, The Divinity School
Duke University
Durham, NC 27706
919/660-3434(B)

Obstetrics/Gynecology

- 1993 Vanessa P. Haygood, MD (*Vice Chair*)
Medical Director, Maternity &
Family Planning for the Guilford
County Health Department and
Private Practitioner
721 Green Valley Road, Suite 101
Greensboro, NC 27408
919/230-1111 (B); 292-7010 (R)

Consumer/Social Science

- 1994 Aida Beshara, PhD
106 Drywood Place
Cary, NC 27513
919/481-2892 (R)

Consumer/Medical Sociology

- 1995 Betty E. Cogswell, PhD
Associate Professor
Department of Family Medicine
Clinical Programs Division
School of Medicine
University of North Carolina
Chapel Hill, NC 27599-7595
919/966-3711 (B); 942-5289 (R)

Public Health

- 1993 Betty H. Dennis, PharmD
Clinical Associate Professor
Pharmacy Practice
School of Pharmacy
University of North Carolina
Chapel Hill, NC 27599
919/962-0030 (B)

* Nonvoting member

January 1, 1993

Internal Medicine

- 1995 Elizabeth S. Mann, MD
Associate Professor
Department of Anesthesiology &
Associate Dean for Admissions
School of Medicine
University of North Carolina
North Carolina Memorial Hospital, 204-H
Chapel Hill, NC. 27599-3355
919/966-5136 (B); 962-8331 (B)

Public Health

- 1994 Tom K. Scott, PhD
Professor, Department of Biology
CB# 3280, Coker Hall
University of North Carolina
Chapel Hill, NC 27599-3280
919/962-3701 (B); 929-1281 (R)

Legal

- 1994 Steven M. Shaber, JD
Jordan, Price, Wall, Gray & Jones
PO Box 2021
Raleigh, NC 27602
919/828-2501 (B)

Burroughs Wellcome Staff

- 1994 Michael D. Rogers, PhD (Ex-officio*)
Senior Clinical Research Scientist
Burroughs Wellcome Company
Post Office Box 13526
Research Triangle Park, NC 27709
919/248-3000 (B)

FHI Staff

- 1994 Evelyn J. Studer, RN, BSN (Ex-officio*)
Institutional Representative
Protection of Human Subjects Committee
Family Health International
Durham, NC 27713
919/544-7040 (B)

ClinTrials Staff

- 1993 B. Randall Vestal, BS (Ex-officio*)
Director, Regulatory Affairs
ClinTrials
Durham, NC 27713
919/544-3900 (B)

M

Family Health International Protection of Human Subjects Committee

Biodata

1. Dennis M. Campbell, BA, PhD, BD - Chairperson

Dr. Campbell received his Bachelor of Arts and PhD degrees from Duke University and his Bachelor of Divinity degree from Yale University. He is Dean of the Divinity School and Professor of Theology at Duke University. Dr. Campbell is a United Methodist minister who has served as a local church pastor, college chaplain, professor, and college and university administrator. He is a Danforth Fellow, an Elder in the North Carolina Conference of the United Methodist Church, and a member of the Board of Ordained Ministry and its Executive Committee. A noted lecturer, seminar leader and author, Dr. Campbell is the author of three books, numerous articles, and reviews in systematic theology and ethics. Through his participation on several major academic boards, Dr. Campbell is a national leader in US higher education. His credentials as an educator and broad experience in the field of theology, coupled with his special interest in ethics, qualify him as a member of the PHSC.

2. Vanessa P. Haygood, MD - Vice Chairperson

Dr. Haygood received her Bachelor of Science degree in biology from Stanford University and her MD from Harvard University Medical School. She received her obstetrical/gynecological postdoctoral training at Duke University Medical Center and is licensed to practice medicine in North Carolina. Dr. Haygood currently serves as the Medical Director of Maternity and Family Planning Services of the Guilford County Health Department and is in private practice as an obstetrician and gynecologist in Greensboro, NC. Since 1986, she has held an academic appointment as Clinical Assistant Professor for the Department of Obstetrics/Gynecology at the University of North Carolina, School of Medicine. From 1982-86, she held an academic appointment as Assistant Professor for the Department of Obstetrics/Gynecology at Duke University's School of Medicine. Dr. Haygood's training and experience in obstetrics and gynecology qualify her as a member of the PHSC.

3. Aida Beshara, PhD

Dr. Beshara received her Bachelor of Arts degree in geography in Cairo, Egypt and her PhD in geography in Durham, United Kingdom. Dr. Beshara held an academic appointment as Professor of the Faculty of Women at Ain-Shams University in Cairo, Egypt for many years and has recently relocated to the United States and resides in Cary, NC. She has published extensively on the subjects of developing countries, the role of women in development, the human environment, regional planning and economics. Her career has included Fulbright sponsorships and assistantships in the United States as well as research and lectures while residing in Afghanistan, Kenya, Syria and India. She has taught and conducted research in the areas of regional planning and development, population planning, women's education and development and urban policy. Dr. Beshara's cultural background and her experience and knowledge of women in developing countries in relation to population and socio-economic issues qualify her as a member of the PHSC.

4. **Betty E. Cogswell, PhD**

Dr. Cogswell received her Bachelor of Arts degree from Goucher College and her Master of Science in Rehabilitation Counseling from North Carolina State University. She earned her PhD in sociology from the University of North Carolina, Chapel Hill. In the past, she has served as Assistant Professor in the UNC Department of Family Medicine and as Assistant Professor in the Department of Mental Health, School of Public Health at UNC. At present, she is an Associate Professor in the Department of Family Medicine at the UNC School of Medicine. She has been active in the fields of family health, consumers' perspectives on health care, women and health, adolescent sexual behavior and population planning. With her professional expertise and extensive knowledge of issues related to women's health, family planning and medical consumers, Dr. Cogswell qualifies as a member of the PHSC.

5. **Betty Hill Dennis, MS, PharmD**

Dr. Dennis received her Bachelor, Master, and Doctor of Pharmacy degrees from the University of North Carolina, Chapel Hill and completed a residency in hospital and clinical pharmacy at North Carolina Memorial Hospital, Chapel Hill. She served as a Research Assistant at UNC and as a Lecturer in the Surgeon's Assistant Program, New Nurse Orientation Program and Radiology Technician Program at NC Memorial Hospital. She also lectured in the School of Nursing at the University of Kentucky Medical Center and was Supervisor of Pharmacy-Central Supply Services for Medicine. Currently, Dr. Dennis serves as a Clinical Associate Professor of Pharmacy Practice at the UNC School of Pharmacy and as a Contributing Lecturer in several Pharmacy, Nursing, and Medical Allied Health Professional courses. She is also the Director of Continuing Education for the School of Pharmacy at UNC. Dr. Dennis' extensive background in the hospital setting and her knowledge of the pharmacy field and practice with patients make her a well-qualified choice to the PHSC.

6. **Elizabeth S. Mann, MD, FACA**

Dr. Mann received her undergraduate degree from Swarthmore College and her MD from Cornell University Medical College. She interned in medicine/pediatrics and completed a residency and a fellowship program in anesthesiology at the University of Virginia Hospital. She is licensed to practice medicine in North Carolina and Virginia. Dr. Mann currently serves as Associate Dean for Admissions, School of Medicine and Associate Professor of the Department of Anesthesiology, University of North Carolina at Chapel Hill. In addition she is the Director of Inpatient Services, Department of Anesthesiology at North Carolina Memorial Hospital. She has conducted several investigative research projects and is the author or co-author of several publications related to the field of anesthesiology. Dr. Mann's medical teaching experience and sensitivity to ethical issues related to research and medical practice qualify her as a member of the PHSC.

7. **Michael D. Rogers, BS, PhD - Ex-officio (non-voting)**

Dr. Rogers received his Bachelor of Science degree in Biology from the University of North Carolina at Charlotte. He then earned a Master of Science in Public Health and a PhD from the University of North Carolina at Chapel Hill in Medical Parasitology. Since 1984 Dr. Rogers has been employed by the Burroughs Wellcome Company where he is currently supervisor of the *Pneumocystis carinii* Biological Research Laboratory. He is a member of the Scientific Research Society of North America, Sigma Xi, the American Society for Microbiology, the American Society of Tropical Medicine and Hygiene, the American Society of Parasitologists and the North Carolina Branch of the American Society for Microbiology. Dr. Rogers' extensive clinical experience with the Burroughs Wellcome Company qualifies him as their staff representative (ex-officio/non-voting) to the PHSC. His presence on the Committee fulfills the function of a qualified and experienced resource of the clinical settings in which Burroughs Wellcome's clinical trials are conducted. As a non-voting institutional representative, he serves as liaison between the investigators and the Committee for the initial and continuing review of research approved by the Committee.

8. **Tom K. Scott, AB, PhD**

Dr. Scott received his AB degree in botany from Pomona College, his MA and PhD in biology from Stanford University. He is currently a Professor in the Department of Biology at the University of North Carolina at Chapel Hill. From 1985-1990, he also served as the Director of the Office of Research Services at the University of North Carolina at Chapel Hill. During this tenure, he established the Committee on the Protection of the Rights of Human Subjects for the College of Arts and Sciences and served as an ex-officio member for three years. He directed a National Institutes of Health/Office of Protection from Research Risks national workshop entitled "Interpreting the Federal Code for Human Subjects Research--the Burden of Protection" in 1991. Dr. Scott's research expertise and experience with institutional review boards in the protection of human subjects qualify him as a member of the PHSC.

9. **Steven M. Shaber, JD**

Mr. Shaber received his Bachelor of Arts degree, Magna Cum Laude, from Wabash College and his Juris Doctor degree from the Duke University School of Law, where he served as the Managing Editor of Duke's Legal Research Program. He has been affiliated with the law firm of Jordan, Price, Wall, Gray & Jones of Raleigh since 1985. The emphasis of his law practice is in general business law, health law and third-party reimbursement, litigation, administrative law, and lobbying. From 1978-85, he served as an Assistant Attorney General, North Carolina Department of Justice. He also has served with the North Carolina General Assembly's Social Services Study Commission. Mr. Shaber is a member of the American Bar Association, serving with the Forum Committee on Health Law, the Litigation Section and the Administrative Law Section. He is also a member of the North Carolina Bar Association, serving as a member of the Administrative Law Committee and the Health Law Committee. Among his other professional commitments, he is currently Secretary/Treasurer of the North Carolina Society of Health Care Attorneys and Chairperson of the North Carolina General Statutes Commission Adoption Law Drafting Commission. His varied experience and background in the legal profession qualify him as a member of the PHSC.

10. **Evelyn J. Studer, RN, BSN - Ex-officio (non-voting)**

Ms. Studer received her Bachelor of Science degree in Nursing from Georgetown University. As an employee of the Washington Home Hospice, Alcoholic Rehabilitation, Inc. and the Arthritis Foundation from 1978-1990, she worked with a variety of patients and clients and is familiar with the special needs of women, the economically disadvantaged, substance abusers, the elderly, and the chronically and terminally ill. She has directed health education outreach programs in addition to working in patient care settings. Currently she serves as FHI's Institutional Representative to the Protection of Human Subjects Committee. In this capacity she is a safety data coordinator and direct channel between the Committee and the investigators and/or the local Institutional Review Boards. Her presence on the Committee fulfills the function of a qualified and experienced resource of the clinical settings in which FHI's studies are conducted. As a non-voting institutional representative, she serves as liaison between the investigators and the Committee for the initial and continuing review of research approved by the Committee.

11. **B. Randall Vestal, BS - Ex-officio (non-voting)**

Mr. Vestal received his Bachelor of Science from Lenoir Rhyne College with a major in chemistry. He completed all course and cumulative examination requirements for a PhD in Medicinal Chemistry at the School of Pharmacy, University of North Carolina, Chapel Hill. Currently he is Director of Regulatory Affairs for ClinTrials. This department works with appropriate governmental agencies involved in the regulation of clinical research. Between 1974 and May 1991, he worked at Burroughs Wellcome Co., most recently in the capacity as Regulatory Coordinator II. His responsibilities involved liaison between the FDA and Burroughs Wellcome for developmental and marketed products. He is a member of the Drug Information Association, Regulatory Affairs Professional Society, Project Management Institute and Sigma Xi. He has co-authored scientific papers in clinical research, drug development and chemistry journals. Mr. Vestal's extensive clinical experience with the pharmaceutical industry and regulatory matters qualifies him as the ClinTrials staff representative (ex-officio/non-voting) of the PHSC. His presence on the Committee fulfills the function of a qualified and experienced resource of the clinical settings in which ClinTrials' clinical trials are conducted. As a non-voting institutional representative, he serves as liaison between the investigators and the Committee for the initial and continuing review of research approved by the Committee.

**Secretary: Marie F. Porter, Administrator, Corporate Affairs,
Executive Office (FHI)**

Appendix III

Policies for the Protection of Human Subjects Committee

Date Issued: March 1, 1993
Date Effective: March 1, 1993
Supersedes: Policy No. 101I Issued April 15, 1992

TITLE

COMMITTEE FOR PROTECTION OF HUMAN SUBJECTS

PURPOSE

To establish a committee to provide guidance on the protection of human subjects.

POLICY

1. The committee to provide guidance on the protection of human subjects is named "Protection of Human Subjects Committee."
2. The Committee shall consist of not less than five (5) or more than ten (10) voting members with a minimum of one each of the following as members:
 - a. Attorney
 - b. Clergy
 - c. Consumer Representative
 - d. Obstetrician/Gynecologist and/or other Physician
 - e. Public Health Representative
 - f. Social Sciences Representative
3. FHI shall be represented on the Committee by one full-time employee who serves as a non-voting member and coordinates the submission of the following to the Committee:
 - safety data reports,
 - adverse experience reports, and
 - study status reports from investigators using the Committee as their institutional review board.

In addition, the institutional representative shall notify each investigator for whom the Committee serves as an institutional review board of the decisions regarding approval of the research protocol and any subsequent amendments. There may be other institutional non-voting members on the Committee who will fulfill these same functions when the Committee reviews studies from other institutions.

4. Committee members shall be selected on the basis of maturity, experience and expertise and appointed by the President, subject to any approvals required by funding agencies.

23

5. Any Committee member who has a conflicting interest in a proposal will abstain from the Committee's deliberations on the proposal except to provide information if requested by the Committee. A member of the Committee who has such a conflict of interest may not vote on the proposal.
6. Members shall be appointed for a term of three (3) years. Terms of office shall be staggered so that not more than three (3) members are appointed in any one year. With exception of the institutional representatives, no member may serve more than two (2) successive terms. In the event of the resignation or death of a Committee member, the President will appoint, subject to any approvals required by funding agencies, a member to serve the unexpired portion of the resigning/deceased member's term.
7. The Chairperson shall be appointed from within the membership of the Committee by the President.
8. The Administrator of Corporate Affairs shall serve as the Secretary of this Committee.
9. The minutes of all meetings of the Committee shall, after approval by the members, be signed by the Chairperson.

Note:

For further information on the protection of human subjects consult 45 CFR Part 46 and 21 CFR Part 50 and 56.



President

P/P-sj/6895

Date Issued: March 1, 1993
Date Effective: March 1, 1993

TITLE

DOCUMENTATION OF CRITERIA FOR PROTECTION OF HUMAN SUBJECTS
COMMITTEE (PHSC) REVIEW OF PROPOSAL SUBMISSIONS
(BIOMEDICAL AND NON-BIOMEDICAL)

PURPOSE

To establish the means for providing criteria for PHSC review of proposal submissions.

POLICY

Documentation shall be provided in the proposal summary that:

1. Risks to subjects are minimized by using procedures:
 - which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
 - whenever appropriate, 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.
3. Selection of subjects is equitable and free of coercion. This includes:
 - description of any modes of advertising that will be used to recruit study subjects;
 - the text of any printed media, radio, TV or telephone ads (attach to the proposal summary); and
 - description of any inducements for study subjects.
4. Provisions have been made to protect the privacy of subjects and to maintain the confidentiality of data.
5. When appropriate, provisions have been made to monitor the data collected to ensure the safety of subjects.

25

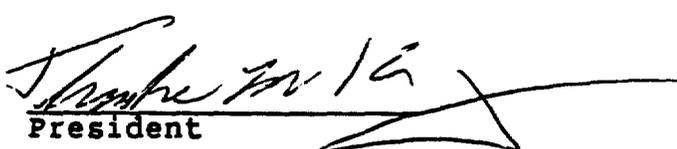
6. When appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence.

In addition:

7. A copy of the informed consent document shall be provided to the PHSC for review. If written informed consent is not furnished for the proposal being reviewed, a request for a waiver shall be submitted to the Committee. This request must explicitly cite which regulations are applicable in justifying the waiver.
8. When available, local (on-site) Institutional Review Boards shall be designated to review study proposals. Any local Institutional Review Board that will review the study shall be specified on the proposal summary.
9. The investigators and sites shall be reported to the PHSC. The qualifying process and criteria should be briefly described in the proposal summary. The sponsoring division shall be responsible for maintaining files of curricula vitae of investigators for each study, which should be available for PHSC review upon request.
10. The PHSC must be knowledgeable about the community from which the subjects are drawn to ensure that their rights will be protected and that the consent process is appropriate for the subject population involved. A brief description of the consideration of the study population and community attitudes shall be included in the proposal summary.

Note:

For further information about criteria for institutional review board approval consult 21 CFR 56.111 and 45 CFR 46.111.


President

P/P-sj/14544

Date Issued: March 18, 1993
Date Effective: March 18, 1993

TITLE

CONDUCTING ACCEPTABILITY RESEARCH STUDIES BY MAIL

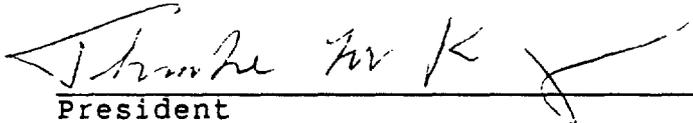
PURPOSE

To define the policy for conducting acceptability research studies and sending study material (products) through the U.S. Postal Service.

POLICY

1. Recruitment for and participation in such studies will be limited to residents of the local tri-county area (specifically Orange, Durham and Wake Counties). Study products may not be mailed directly to participants in other states or countries.
2. One, to a maximum of three (one per county), full service medical clinic(s) will be contacted and enlisted to provide medical services to study participants requiring medical attention related to the use of the study products. Referral to any of these clinics will be made by the Corporate Director of Medical Affairs or, in his absence, other licensed FHI medical staff.
3. Only studies that have been designated by the PHSC as "non-significant risk" to participants will be conducted in the manner described above. Risk determination will be based on results of product toxicity and safety data and/or selection of participants who are practicing reliable contraception, are sterilized and are practicing monogamy. When prototype devices (non-FDA approved products) are utilized, these studies must be conducted under an abbreviated Investigational Device Exemption (IDE) and in accordance with these regulations.
4. Only studies evaluating product acceptability, consumer preference or product function will be conducted in this manner. Efficacy and safety of study products will not be evaluated through the practice described above.

5. Study products sent through the U.S. mail will be limited to chemical and physical barrier methods and include: commercially available spermicides, female condoms, and male latex and plastic condoms. Study products requiring prescription or special fitting (e.g. diaphragm or cervical cap) are excluded from the list of study products which FHI can distribute to participants by mail.
6. "FDA approved products" or "investigational devices" may be utilized in these studies provided that the study is designated and approved by the Protection of Human Subjects Committee (PHSC) as "non-significant risk" to participants.
7. Informed consent forms that are mailed and signed without benefit of a witness will be subject to internal FHI (RA/A) audit to verify that: (1) consent forms are signed by both partners; (2) both partners have responded correctly to all queries regarding study eligibility; and, (3) consent forms are dated.



President

P/P-sj/14884

Appendix IV

Protection of Human Subjects Committee Forms

- 1. Proposal Summary**
- 2. Reviewer's Checklist**
- 3. Certification of Approved Research Proposal**
- 4. PHSC Adverse Experience Report**
- 5. Study Status Report to the PHSC**

PHSC/Proposal Summary

Page Two

PHSC Proposal #:

10. Institutional Review Board (IRB) review (see section 2)
11. Brief description of how study population and community attitudes were considered for this research project (to insure protection of rights and that the consent process is appropriate to the subject population):
12. Statement of procedures involving study subjects; which procedures are experimental? How are the procedures (a) consistent with sound research design, (b) not exposing subjects unnecessarily to risk and, (c) whenever possible, already being performed on the subjects for diagnostic or treatment purposes?
13. Summarize the risks, if any, to the subjects [e.g., drugs, devices, venipuncture, biopsy, other invasive procedures (includes privacy-related), recordings, photography, video]:
14. Summarize the benefits, if any, for the subjects:
15. How are the risks reasonable in relation to:
 - anticipated benefits (if any) to subjects, and
 - the importance of the knowledge that may reasonably be expected to result from the study?
16. What provisions have been made to protect the privacy of the subjects and to maintain the confidentiality of the data?
17. When applicable, what provisions have been made to monitor the data collected to ensure the safety of the subjects?
18. When applicable, what additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence?

PHSC/Proposal Summary
Page Three
PHSC Proposal #:

19. Informed consent:

Written _____ Oral _____

Grade level, using the Fry Graph _____

When consent forms are translated into foreign languages, a statement will be furnished to the PHSC attesting to the accuracy of the translation.

[If a copy of the written informed consent document is not furnished for the proposal being reviewed, a request and reason for a waiver shall be submitted to the PHSC. This request must explicitly cite which regulations (Federal or other) are applicable in justifying the waiver.]

20. Mode of advertisement (applicable to international and domestic studies): How will study subjects be recruited/enrolled (describe recruiting procedures below)? The text of any ads must be attached to the proposal summary.

___ Investigator recruitment, specify:

___ Printed media (e.g., newspapers, posters, etc.)

___ Telephone

___ Contract or recruiting agency

___ Other, specify

___ To be determined (Note: Expedited review submission to the PHSC Chair permitted between committee meetings.)

**FAMILY HEALTH INTERNATIONAL
PROTECTION OF HUMAN SUBJECTS COMMITTEE
Reviewer's Checklist**

Proposal # _____ Title: _____

1. Study design: (see attached Proposal Summary and Protocol) ADEQUATE INADEQUATE

- a. Statement of purpose of study _____
- b. Research plan (methods, site, duration) _____

Comments: _____

2. Benefits and risks of study (see attached Proposal Summary and Protocol)

- a. Anticipated benefits clearly defined _____
- b. Foreseeable risks clearly defined _____
- c. The research design cites the foreseeable risks to subjects that are minimized and reasonable in relation to anticipated benefits. _____

Comments: _____

3. Selection of subjects (see attached Protocol)

- a. Selection of subjects reflects equitability _____
- b. Selection of inclusion criteria _____
- c. Selection of exclusion criteria _____
- d. Remuneration or inducement plan _____

Comments: _____

4. Informed consent (see attached Protocol)

- a. The Fact Sheet and Volunteer Agreement adequately describe the study and state the foreseeable/unforeseeable risks and anticipated benefits of the research plan. _____
- b. Applicable practices and procedures designed for the protection of the rights and welfare of the subjects _____
- c. Procedures for obtaining legally effective informed consent _____
- d. Provision of whom to contact for answers to research-related questions, the subject's rights or in the event of a research-related side effect _____

Comments: _____

5. Recommendation: a) approve _____ b) disapprove _____ c) defer _____

6. Recommended reporting frequency: a) annually _____ b) semi-annually _____ c) quarterly _____ d) other (specify) _____

7. Reviewer: _____ Date: _____

34

FAMILY HEALTH INTERNATIONAL

PROTECTION OF HUMAN SUBJECTS COMMITTEE

Certification of Approved Research Proposal

Date/PHSC Meeting _____ Proposal No. _____

Title _____

In the opinion of the FHI Protection of Human Subjects Committee:

- a. The risks of the subjects are so outweighed by the sum of the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to accept the risks involved in this research activity.

Yes _____ No _____ Comments _____

- b. The rights and welfare of the subject are considered adequately protected.

Yes _____ No _____ Comments _____

- c. The procedure for obtaining legally effective informed consent by adequate and appropriate methods is satisfactory as outlined.

Yes _____ No _____ Comments _____

- d. Other comments or advice pertinent to the conduct of this research activity.

Committee recommendations:

- a. In the judgment of the Committee the study proposed should be approved as stated above.

- b. In the judgment of the Committee this study should be approved with the following modifications: _____

The Protection of Human Subjects Committee wishes to review the study:
annually _____ semiannually _____ quarterly _____ other (specify) _____

The Protection of Human Subjects Committee is to be informed of any death, serious, and/or life-threatening unexpected adverse events during the course of the study as soon as relevant information is obtained.

- a. Human Subjects: Reviewed, not at risk _____
Date

- b. Human Subjects: Reviewed, at risk, approved _____
Date

Reviewed and approved on behalf of the PHSC:

Dennis M. Campbell, Chairperson Date

36

Family Health International
Protection of Human Subjects Committee

PHSC

Preliminary Notification Form for Adverse Experiences that are:

•Fatal, or •Life-Threatening, or •Serious and Unexpected

Center name _____ and number: _____

Study name _____ and number: _____

Patient Order or Screening number: _____

When was patient first given drug/device in this study? ____ / ____ / ____
day month year

Describe Adverse Experience: _____

When did Adverse Experience start? ____ / ____ / ____
day month year

Patient's current status: Recovered__ Sequelae Present__
Adverse Experience Still Present__ Patient Died__

When did Adverse Experience stop(or patient die)? ____ / ____ / ____
day month year

Related to Investigational Product: No__ Probably Not__ Possibly Yes__ Probably Yes__

Action taken regarding study product: None__ Use Interrupted__
Discontinued ____ / ____ / ____
day month year

Describe treatment given: _____

Documentation Attached: Hospitalization Summary__ Pathology Report__
Operative Report__ Laboratory Report__ Autopsy Report__
Other _____

Signature of Investigator _____ Date of Signature _____

FAX [919/544-7261] OR AIRMAIL TO:
FHI Institutional Representative,
Protection of Human Subjects Committee
Family Health International
P.O. Box 13950, Research Triangle Park Branch
Durham, NC 27709 USA

Note: An Adverse Experience (AE) Form must also be filled out in addition to this Preliminary Notification.

Family Health International

Study Report to the Protection of Human Subjects Committee (PHSC)
For Investigators Using the PHSC as their Institutional Review Board Only

All investigators using the PHSC as their Institutional Review Board must submit a status report on an annual basis dating from the initiation of the study. In addition, a final study report must be submitted after study termination.

Study name _____ and number: _____

Investigator name _____

Center name _____ and number: _____

Date of this report: ___ ___ / ___ ___ / ___ ___
day month year

Status of study: ___ ongoing
___ final report

As of the date above:

Total number of subjects enrolled into study: _____
Total number of subjects who terminated early from the study : _____
Total number of subjects who have completed the study: _____

Please list any subjects who terminated early from the study because of an Adverse Experience since the date of your last PHSC report.

Table with 4 columns: Patient ID Number, Date of Admission, Date of Termination, Adverse Experience Which Caused Termination. Includes multiple rows for data entry.

Please note--any adverse experience that is:
•fatal, or
•life-threatening, or
•serious and unexpected
must be reported immediately on a PHSC Notification Form.

Signature _____ Date of Signature _____

Name and Title: _____

SEND TO: FHI Institutional Representative
Protection of Human Subjects Committee
Family Health International
P.O. Box 13950, Research Triangle Park Branch
Durham, NC, 27709, USA

Appendix V

**Declaration by Member
of FHI Protection of Human Subjects Committee
Regarding Conflicts of Interest**

FAMILY HEALTH INTERNATIONAL

DECLARATION BY MEMBER OF
PROTECTION OF HUMAN SUBJECTS COMMITTEE
REGARDING CONFLICTS OF INTEREST

Operating Guidelines for the Protection of Human Subjects Committee provide at Section IV.6. and at Appendix III:

Any Committee member who has a conflicting interest in a proposal will abstain from the Committee's deliberations on the proposal, except to provide information if requested by the Committee. A member of the Committee who has such a conflict of interest may not vote on the proposal.

Examples of potential conflicts of interest of a Committee member with respect to any research proposal to be considered by the Committee include:

1. A member or a member's spouse or dependents having personal equity holdings or options in any company that would be affected by the outcome of the research or that produces a product or equipment being evaluated in the research project. This prohibition does not include blind trusts, diversified mutual funds, or other financial interests over which the investor has no discretionary control. The Committee may grant a waiver of this requirement if it determines that such holdings are so insignificant as not to create a conflict of interest.
2. A member who receives fees for service or honoraria from a private source if the research involves the evaluating or testing of a product of the source.
3. A member who serves as an officer, board member or in another management position of a private source or company that would be affected by the outcome of the research or that produces a product or equipment being evaluated in the research project.
4. An institutional non-voting representative on the Committee is deemed to have a conflict of interest on any research proposal for which the representative has direct responsibility as an employee of the institution.

The undersigned Member of the Protection of Human Subjects Committee hereby acknowledges conflicts of interest may arise. Member agrees that, should a conflict of interest arise, Member will so advise the Committee Secretary in writing or orally in the presence of Committee members, shall abstain from the Committee's deliberations on the research proposal at issue except to provide information if requested by the Committee, and will not vote on the proposal.

PHSC Committee Member

Date

NOTE: Approved/implemented by the FHI Protection of Human Subjects Committee (PHSC), February 23, 1990. This form is to be signed by all PHSC members at the first committee meeting of each calendar year.

Appendix VI

Informed Consent Procedures

Informed Consent Procedures

FAMILY HEALTH INTERNATIONAL
PROTECTION OF HUMAN SUBJECTS COMMITTEE
Informed Consent Procedures

I. RESEARCH COVERED UNDER 45 CFR 46 (Common Rule)

The Office for Protection from Research Risks of the National Institutes of Health, Department of Health and Human Services, lists two instances, (c) and (d), under which an IRB **may approve a consent procedure which alters, some or all of the elements of informed consent** set forth in 46.116 (a) and (b), or **waive the requirement to obtain informed consent** provided the IRB finds and documents that:

- (c)
 - (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 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; and
 - (2) the research could not practicably be carried out without the waiver or alteration.
- (d)
 - (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.

§ 46.117 gives the specifics for **documentation of informed consent**:

- (a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized 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. 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 an 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.

II. RESEARCH COVERED UNDER 21 CFR 50 and 56 (US/Food and Drug Administration regulations)

Sec. 56.109(c) states that an IRB shall require documentation of informed consent in accordance with Sec. 50.27, except that the IRB may, for some or all subjects, **waive the requirement that the subject or the subject's legally authorized representative sign a written consent form** if it finds 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 the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Sec. 50.27 addresses the **documentation of informed consent**:

- (a) Except as provided in Sec. 56.109(c), 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 Sec. 56.109(c), the consent form may be either of the following:
 - (1) A written consent document that embodies the elements of informed consent required by Sec. 50.25. 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.
 - (2) A "short form" written consent document stating that the elements of informed consent required by Sec. 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there should 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 the 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.

2/11

Essential Elements of Informed Consent Checklist

Essential Elements of Informed Consent Checklist

Potential subjects must be given all information that might reasonably be expected to influence their willingness to participate. This information should be provided in language understandable to the subject or the representative.

Introduction

__ A simple explanation of the informed consent process.

Reason for the Study

__ A statement that the study involves research.

__ An explanation of the general purposes of the study.

__ When applicable: a description of the importance of the knowledge that may be reasonably expected.

General Information about the Study Methods/Product/Drug

__ A description of the study methods, procedures, products or drugs.

Your Part in the Study

__ A statement concerning the expected duration of the subject's participation, frequency of trips to the study site, etc.

__ A statement concerning the approximate number of subjects involved in the study.

__ An explanation of the procedures to be followed and identification of those which are experimental.

Possible Risks and Benefits

__ A description of all reasonably foreseeable discomforts and risks to the subject.

__ When applicable: 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.

__ A description of benefits to subjects that can reasonably be expected.

If You Decide Not to Be in The Study

__ A statement that the subject is free to refuse to participate in the study at any time without penalty and without jeopardy.

__ When applicable: options available for medical care/treatment if the subject decides not to participate in the study.

Confidentiality

- A statement describing how confidentiality will be maintained and who will have access to the data.

Compensation

- A statement of any costs to the subject that may result from participation in the study, if there are any.
- When applicable: a statement about any monetary or other inducements for participation and how these will be prorated for subjects who do not complete the entire study.

Staying in the Study

- If there are requirements for participation or continued participation in the study, (such as exclusive use of specific drugs, devices or treatments) state them in this section.
- When applicable: a statement that significant new findings developed during the course of the study which may relate to the subject's willingness to continue participation will be provided to the subject.

Leaving the Study

- A statement that the subject is free to withdraw from the study at any time without penalty and without jeopardy.
- List any reasons why subjects may be asked to leave the study.
- When applicable: the consequences of a subject's decision to withdraw from the study and procedures for orderly termination of participation by the subject.

Contact for Questions

- Whom to contact (name, phone number) if subjects have further questions about the study.
- Names, phone numbers and, if applicable, addresses of Institutional Review Board contact persons if subjects have questions about their rights while they are in the study. If the PHSC is serving as the only review board, list Evelyn Studer, Institutional Representative, as the contact person for FHI studies.

If You Have a Problem

- Whom to contact, with telephone numbers, if the subjects have any problems they think are related to their participation in the study.
- If such a problem should occur and they need more help, what will happen and who is responsible for payment?

Note: No informed consent 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, sponsor, the institution or its agents from liability for negligence.

Informed Consent Model
(Boiler Plate Text)

**FAMILY HEALTH INTERNATIONAL (FHI)
INFORMED CONSENT**

Name of Study:
Principal Investigator:

Introduction

This Consent Form contains information about the study named above. In order to be sure that you have all the facts about being in this study, we are asking you to read (or have read to you) this Consent Form. You will also be asked to sign it (or make your mark in front of a witness). This study has been approved by the ethics review committee(s) of FHI and (*if applicable, a local review board*). We will give you a copy of this form.

Reason for the Study

You are being asked to take part in a research study to (*objectives of the study in easily-understood words*).

General Information about (*the Study Methods/Product/Drug*)

(*General information about the study methods/procedures/product(s)/drug(s) to be taken or used in the study.*)

Your Part in the Study

Your part in the study will last _____. About (# *women/men/couples*) will take part in this study (*specify at this site and/or at # of sites.*)

If you agree to be in the study, you will (*an explanation of the tests, procedures, follow-up, etc. that will be required and identification of those which are experimental, in easily-understood words*).

Possible Risks and Benefits

(*Specific language for each type of study. If necessary, Risks and Benefits may be placed into separate subsections to avoid a potentially confusing document.*)

If You Decide Not to Be in the Study

You are free to refuse to be in this study.

(When applicable: There are other methods of (treatment/birth control) available. (*List them.*) You may discuss these other methods with the clinic staff before making your decision. You may choose any of these other methods, as long as you have no health problems that would cause us to advise against them.

Confidentiality

To protect your privacy, forms which are sent out of this site as part of the study will not show your name. If the results of this study are published, your name will not be shown. However, the staff of FHI (*and/or the United States Food and Drug Administration, and/or other sponsoring organizations*) may sometimes look at records kept at this site.

When applicable: If you miss a study visit, the clinic staff may contact you at home by phone, mail or in person to schedule another visit and to see if you still want to be in the study.

Compensation

You will not be paid, since you do not have to be in this study. (*If payment is planned, tell volunteer the actual amount to be given, conditions for receiving this payment, and when payments are made.*)

Staying in the Study

When applicable: If you decide to be in the study, we ask you to use only the study (*drug, device or treatment*) which we provide. (*Or if the study method is to be used with another method, list conditions of use. Also note any exceptions to the exclusive use requirement.*)

Leaving the Study

You may leave the study at any time.

When applicable: If so, please tell the doctor or clinic staff why you wish to leave.

Also, you may be asked to leave the study if (list applicable points):

- the doctor feels it is best for you, or
- you are not able to follow the study procedures, or
- the study is stopped.

When applicable: We will tell you if we learn something new about the (*study product or drug*) that could affect your choice to stay in the study. When you are no longer in the study, you will still be able to use this clinic.

Contact for Questions

Please contact (name and number) if you have any problems or questions about this study. If you have any questions about your rights while you are in the study you may contact (name, phone number and address of local Institutional Review Board (IRB) representative or, if FHI's PHSC is serving as the IRB: Evelyn Studer, Institutional Representative, Protection of Human Subjects Committee, phone number and address).

VOLUNTEER AGREEMENT

When applicable: I know that I must not use any other method of birth control while I am in the study (*if method is to be used with another method, say so here*). I know that even if I use the study method in the correct way there is a chance that I may get pregnant. If I think I am pregnant, or have any problems while I am in the study, I will tell the doctor at once. The study, as well as its risks and benefits, has been explained to me. Dr. _____ or Dr. _____ will care for my health while I am in the study.

The above document describing the benefits, risks and procedures for the study titled (name of study) has been read and explained to me in my native language, (*specify*). I agree to participate as a volunteer.

Date

Signature of Volunteer /Subject's Representative

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research study have been explained to the above individual.

Signature of Investigator or Designee Who Obtained Consent

For Illiterate Volunteers:

I was present while the benefits, risks and procedures for the study titled (name of study) was read to the volunteer. All questions were answered and the volunteer (or his or her legal representative) signed to agree to take part in the study.

Date

Signature of Witness (Patient's Representative)

Recommendations from Seminar on Readability & Comprehensibility of Text
(Conducted by Prof. Alan Crawford, September 9, 1992)

13

Recommendations from Seminar on Readability and Comprehensibility of Text

Over the last several years, The Clinical Trials Division and the Protection of Human Subjects Committee have made important contributions in producing an Informed Consent document that is readable and comprehensible. Building on the progress made by using the SMOG index to standardize the readability grade levels of these documents, FHI recommends the Committee's endorsement of the following tools to refine the accuracy of readability measurements:

1. Since the Fry graph is more widely accepted and favored legally, use this graph to measure the reading grade level of Informed Consent documents. By using graph systems for both, the English and Spanish measurements would be more comparable.
2. Adopt the following measures to increase the accuracy of the reading grade level determination:
 - Non-technical long words that are really combinations of short words such as motorcycle and bookkeeper would be counted as two words.
 - Words that have been made into three syllables by the addition of *-er*, *-ed*, or *-es* such as *researcher*, *created* and *trespasses* would be counted as two syllables.
 - After the explanation and/or definition of proper nouns, technical terms or abbreviations in the text (such as FHI, IUD or vasectomy), these words would be counted as one syllable.
3. Use of the Crawford Graph to measure the grade level of Informed Consent documents in Spanish.

While *readability* measurements are useful to assess the surface structure features of a document, *comprehensibility* is the primary goal in producing text that is understandable to the reader. An Informed Consent document is only as useful as its ability to be understood by the reader. In order to protect the safety and rights of human subjects, attention must be paid to the content and meaning of the document. While it is desirable to use shorter words and sentences, the precision of the concepts should never be sacrificed.

FHI also recognizes that informed consent is a whole process with the document itself serving only as the legal "evidence". The clinic personnel play an extremely important role in presenting background information and explanation for any unfamiliar concepts.

FHI recommends that the Committee promote the importance of comprehensibility by endorsing the following:

1. Recommendation of a range of grade levels suitable to the complexity of the Informed Consent document and the educational level of the subjects. Grade 6 would be recommended for developing countries and grades 6-8 for developed countries.
2. Promotion of the recommendations presented by Dr. Crawford on writing "Friendly" Text.

Writing "Friendly" Text
Alan N. Crawford, California State University, Los Angeles

Use active voice instead of passive voice.

Use personal pronouns.

Write in the first person.

Help readers make connections by using conjunctions, such as *because, when, so that*.

Use fewer embedded clauses so that you can keep kernel sentences intact. For example, "Because he was tall, John reached to the high shelf." instead of "John, because he was tall, reached to the high shelf."

Explain difficult ideas and define difficult terms in the text.

State the purpose of text.

Highlight important ideas
by placing them in boxes.

Use **bolding**, underlining and *italics*.

Subheadings

Use subheadings.

- Use bullets for items in a series; then arrange them vertically on the page.

How can you highlight key issues? Focus on key issues with a question; then answer the question.

Use analogies and examples to build background knowledge.

Minimize conceptual density.

Use metadiscourse, i.e., talk to the reader in the text. For example, "Be sure to follow the directions exactly, because if you don't..."

But, avoid cluttering the page with too many devices; i.e., don't get too fancy.

56

Appendix VII

Definition of Terms

Definition of Terms:

"Assent" means a child's affirmative agreement to participate in research.

"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.

"Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

"Human subject" refers to a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or uses identifiable private information including the observation or recording of behavior. In some cases, a human subject is an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be a healthy human or a patient (person who is a recipient of treatment).

"Informed consent" means consent by a subject to participate in an experiment or study after achieving a full understanding of what is involved in the study.

"Institutional Review Board" (IRB) means any board, committee or other group formally designated by an institution to review research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.

"Intervention" includes physical, social, and behavioral procedures by which data are gathered and manipulations of the subject's environment that are performed for research purposes.

"Interaction" includes communication or interpersonal contact between investigator and subject.

"Minimal risk" means the probability and magnitude of harm or discomfort anticipated in the proposed 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.

"Parent" means a child's biological or adoptive parent.

"Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

"Research" means a systematic investigation designed to develop or contribute to generalizable knowledge.