Hazelden Betty Ford Foundation

Butler Center for Research
RESEARCH POLICY MANUAL

Dedicated to improving recovery from addiction by conducting clinical and institutional research, collaborating with other research centers, and communicating scientific findings

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1. Introduction to research at Hazelden Betty Ford Foundation

The Butler Center for Research (BCR) is dedicated to improving recovery from addiction by conducting clinical and institutional research, collaborating with other research centers, and communicating scientific findings. As a division within the Hazelden Betty Ford Foundation (HBFF), the BCR informs and improves HBFF's delivery of services for individuals, and produces research that benefits the field of addiction. BCR staff members serve as consultants on research projects commissioned by the Board, organization President, and Recovery Services.

Consistent with HBFF's mission, vision, and values, BCR is committed to patient care and confidentiality. Research is focused on improving recovery services, and the right of patient participants to engage in treatment without research interference is essential. In addition, BCR is committed to participant confidentiality. All research records are stored in locked and secured files and protected according to current federal confidentiality statutes.

This manual establishes policies to help HBFF pursue its commitment to research. HBFF is particularly committed to applied research that will help the organization, and the greater field of addiction treatment, understand pathways of recovery. The policies in this manual are created to ensure that research is committed with scientific integrity, and that the rights of human subjects are maintained at all times.

Current studies

At the time of the most recent revision of this manual, BCR staff members were involved in various research projects, including, an outcomes study for Twelve Step treatment of opioid addiction, an evaluation of treatment outcomes for legal professionals, and research regarding cravings among patients taking various medications during recovery. BCR researchers also partner with other research organizations when specific expertise is need for planned studies, such as knowledge of a special population or new methodologies.

About the Hazelden Betty Ford Foundation

Mission: *We are a force of healing and hope for individuals, families and communities affected by addiction to alcohol and other drugs.*

Vision: *Together, we will overcome addiction.*

Values:

- **Respect** - Treat every person with compassion, dignity and respect
- **Science -** Treat addiction as a family disease using evidence based practices that address the mind, body and spirit
- **Recovery -** Commit to the Twelve Step principles including abstinence-based recovery
- **Leadership -** Innovate and demonstrate the courage to change
- **Growth -** Pursue personal and professional growth in ourselves and others
- **Service -** Be of Service
- **Teaching -** Be the leader in education, advocacy and dissemination of addiction knowledge

2. Research proposal review

2.1 Compliance with the Common Rule (45 CFR 46)

Title 45 Code of Federal Regulations Part 46 Protection of Human Subjects (45 CFR 46, also known as the "Common Rule") requires that all research involving human subjects follow federal policies and guidelines for the protection of human research subjects. Further, the federal government requires all research organizations that conduct federally funded or regulated research to obtain either a multiple project assurance (MPA) or a single project assurance (SPA). Large research entities like universities or government agencies typically have MAPs that cover all human subjects research within the organization. Smaller organizations like community hospitals or mental health clinics may obtain a SPA if conducting federally funded or regulated research. This agreement, negotiated by the Office of Human Subjects Protection, National Institutes of Health, covers only the specific project funded and assures that the research organization will follow the provisions of 45 CFR 46. See Appendix B for specific provisions. To request a SPA application, contact the Office of Human Research Protections (OHRP) at (866) 447-4777 or via email at OHRP@hhs.gov. BCR maintains a federalwide assurance document (FWA) with OHRP that is currently valid through May 2020. To date, there is no internal Institutional Review Board (IRB) at HBFF; research is reviewed and approved by a federally-reviewed external IRB that has been established in the current OHRP-approved FWA. The OHRP signing official for BCR research is the Executive Director of the BCR (or an appropriate individual designated by him/her).

2.2 Research Action Team and Privacy Board

In lieu of a formal internal IRB, the Research Action Team and Privacy Board (RAT/PB) aims to fulfill the intent and duties of an IRB, as described by the policies set forth in the Common Rule, within HBFF's existing competencies and resources. ***The RAT/PB is not a substitute for IRB review for human subjects research, as defined by the Common Rule. Researchers attempting to conduct human research must obtain additional approval from a federally-recognized IRB before engaging in research activities.*** The RAT/PB will follow the rigorous policies for human subjects research protections in order to establish a best practices model for ensuring the scientific merit, privacy, and safety of all research conducted by the BCR or any research requiring the engagement of HBFF staff or patients.

In accordance with the Common Rule, the RAT/PB is comprised of a minimum five (5) members, each with one vote to cast for all decisions. Members must have adequate experience or expertise to make appropriate decisions regarding proposed research projects. These members cannot be all of the same profession or sex, and all efforts should be made to ensure that members are racially and culturally diverse. At least one (1) member must have primary concerns in scientific areas, and at least one (1) member must have primary concerns in nonscientific areas (e.g. counselors or members of the clergy). One member must be not otherwise affiliated with HBFF, except in their role on the RAT/PB, nor can they be an immediate family member of someone affiliated with HBFF. No RAT/PB member may cast a vote in a review of research that they are personally involved with as a member of the research team, although they may attend meetings in order to provide additional information regarding the study, when necessary/appropriate. RAT/PB decisions can only be made when a majority of members are present. Decisions are made through a consensus when possible. If a consensus is not reached, a democratic voting process is implemented with majority rule. The RAT/PB is chaired by the BCR Executive Director or his/her designate.

2.3 Research category and review process

Research definition

According to the Common Rule, Subpart A, subsection 46.102, research is defined as "*a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge"*. Not all of the projects conducted by BCR constitute research. Evaluation that is not intended to produce generalizable results or theories is considered "routine evaluation", and is not subject to the same federal policies as research. Routine evaluation does not involve experimental design, changes to routine treatment, and does not result in external publication. Instead of trying to explore broad theories that may be applied to the entire field of addiction and treatment, routine evaluation only provides information for a specific program or service (an example is a patient satisfaction questionnaire or educational program surveys). The RAT/PB still reviews routine evaluation projects, but they are not held to the same rigorous standards as research projects.

Research requiring RAT/PB review/approval

- Research by non-HBFF staff
    - If a person not affiliated with HBFF intends to conduct a research project using HBFF patients as subjects, or they wish to use information from HBFF patient record systems, a proposal describing the intended research must be submitted to the RAT/PB for approval. A proposal template form is included in Appendix C.
- Research by HBFF staff
    - If a staff member in any HBFF department, program, or service wishes to conduct a research project involving current or past HBFF patients or their records, RAT/PB approval is required if any of the following conditions occur:
        - New information is to be used. If the intent is to collect new data (via questionnaires, interviews, or tests), the project must be reviewed.
        - The project involves intervention. A research project that exposes patients to new treatments or activities must be reviewed. This includes elimination or reduction of any routine treatment components.
        - The project involves interaction. If a research project involves interaction with HBFF patients, such as in-person or telephone interviews, the project requires review.
        - The method includes assignment to different treatment groups, so that not all participants have equal risk or potential benefits from participation.
        - Outside funding supports part or all of the project. A research project that receives funds from organizations other than HBFF to support all or part of the intended work must be reviewed.

- Publication of results to non-HBFF audiences is expected. If a research project will include dissemination of study results in the form of a written report or article to persons other than HBFF staff or Board of Directors, it must be reviewed.

- Research will be conducted with protected populations. OHRP designates the following as protected populations: 1) Pregnant women, human fetuses, and neonates; 2) Prisoners; and 3) Children. Additionally, if a research project includes among its participants a vulnerable group (people who are at high risk for coercion), such as military, cognitively-impaired people, or homeless people, the project must be reviewed.

Research NOT requiring RAT/PB approval

The RAT/PB need not review research projects involving existing data sources, with no outside funding and no intention to disseminate a written report to non-HBFF audiences. The intended project must be approved by the supervisor of the staff member who plans to undertake the study before work commences. In addition, all identifying information must be removed from the database and project files. This includes, but is not limited to patient names, social security numbers, history and record numbers.

Federal regulations specifically state that the following types of research are exempt from 45 CFR 46: education instructional strategies or effectiveness, educational tests without participant identifying information or possibility of harmful criminal or civil consequences upon release of research information, if participants are public officials or candidates for public office whose research information will be kept confidential during and after research completion, existing data is used without identifying information, and taste and food quality research where good are deemed safe for consumption.

If individuals planning to undertake a research project are uncertain about whether it meets the criteria for review, they should consult with the chair of the RAT/PB.

2.4 Research review process

The RAT/PB reviews all proposed research projects that include HBFF patients or clients. The team reviews research proposals by HBFF staff members and affiliated parties to ensure that research proposals protect patient/subject rights and that the methods are scientifically sound. Consistent with ethical principles of research and the Belmont Report (see Appendix A), the RAT/PB is specifically charged with ensuring that research participation is voluntary and informed, possible benefits are maximized and harm is minimized, and that the benefit and burden of research are justly applied.

To this end, the RAT/PB carefully considers each proposal to ensure that participants' rights are respected. For projects that involve potential disruptions to the treatment process (interviewing patients, administering tests, observing treatment), the final decision on HBFF's participation in the research will be made in consultation with appropriate clinical staff. If projects will not disrupt patients in treatment (i.e. only include existing patient records), then the final decision on HBFF's participation will be made by the RAT/PB.

Research review protocol

1. Proposal is submitted to the RAT/PB Chair

2. Chair conducts initial review in order to:

    a) Verify that each required component is addressed adequately. Researcher may be asked to furnish more information and resubmit the proposal if the Chair determines that components are not addressed thoroughly.

    b) Determine if proposed research meets minimum requirements for scientific integrity, utility, and feasibility. Proposals not meeting minimum requirements will be returned to research with written explanation for decision. Researchers are free to submit a revised proposal.

3. After the initial review, the Chair sends proposal out for review to a minimum of three members of the RAT/PB qualified to judge the merits of the specific proposal. For proposals that involve possible disruptions to the treatment process, appropriate clinical staff will be asked to review the feasibility of the project.

4. Reviewers report back to the Chair, verbal or in writing, concerning any questions for the research and/or a recommendation on HBFF's participation in the project.

5. Chair contacts researcher to obtain answers to any questions raised during the review process.

6. Chair summarizes proposal and results of proposal review process for RAT/PB. The team may decide to:

    a) approve the research proposal;
    b) approve the research proposal with revisions;
    c) to table the research proposal until the researcher provides further information or clarification before making a decision; or
    d) disapprove a proposal.

If the RAT/PB decides to disapprove a research proposal, it shall include in its written notification a statement of reasons for the disapproval. The researcher is then free to submit a revised proposal to the RAT/PB for another review.

Right to disapprove or terminate research

The RAT/PB Chair or his/her designate may discontinue any research project at any time if he/she believes the research poses a risk to patients or to HBFF.

Proposal review questions

In accordance with 45 CFR 46 (the Common Rule), the RAT/PB will use the following questions as a guide for properly reviewing all research proposals:

1. Are human participants protected?

a. Are risks to human subjects minimized?
b. Have adequate safeguards been made for the protection of human subjects involved in the research?

c. Are risks to human subjects reasonable?

d. If experimental manipulation of human subjects is involved, how will they be protected from undue harm?

e. Do potential benefits of the research justify any risks to human subjects?

f. Is selection of subjects equitable?

g. Are vulnerable populations protected? If so, how?

h. How will informed consent be obtained from potential subjects? Does it contain ALL of the following required elements?
   - a statement of purpose
   - a description of anticipated risks and discomforts
   - a description of potential benefits
   - disclosure of appropriate alternative treatments
   - a statement of confidentiality
   - information regarding availability (or lack thereof) of compensation for injuries
   - contact information for the investigator(s) and human rights protection board
   - an explicit statement of the right to refuse participation and the voluntary nature of the study

i. Are there adequate provisions for monitoring participant safety, as necessary?

j. Are there adequate provisions for protecting subject confidentiality? How will confidentiality be ensured?

2. Is the proposed research technically sound?

   a. Does the proposed study design and methods meet minimally accepted standards for conducting scientific research?

   b. Do measurement tools have established reliability and validity? (Or is the purpose of the study to evaluation reliability and validity of an instrument?)

   c. Is the sample size appropriate?

   d. Is the statistical analysis plan appropriate?

   e. Is the researcher experienced and knowledgeable about previous research that has been done on the topic?

f. Has the previous research on the topic been published in refereed journals or conferences? Is the research based on a line of inquiry generally accepted by mainstream scientists and academics?

g. If the research is based on a new line of inquiry, has the researcher built a solid foundation of related research through a thorough literature review?

3. Is it likely that the proposed research can be carried out successfully?

   a. Is the research plan feasible?

   b. Do the investigators have the resources and capabilities to do what they propose?

   c. Do the investigators have the appropriate credentials and experience to do what they propose? If not, are they being supervised by someone who does?

4. Is the proposed research likely to be of value or significance by yielding useful results?

5. Has approval for the project been obtained from the appropriate parties?

   a. Has the investigator received approval from the director (or equivalent) of the unit, division, program, or agency in which he/she intends to conduct the research?

   b. If the investigator is a researcher from an outside agency, has he/she received approval from his/her Institutional Review Board?

3. Research monitoring and event reporting

To ensure that approved protocols are followed and that human subjects' rights are protected, researchers must be in contact with the RAT/PB Chair annually. If deemed necessary by the Chair, the research project may require additional, more rigorous monitoring procedures.

3.1 Routine monitoring

Routine monitoring includes annual updates to the RAT/PB Chair regarding the status of approved research projects. Annual routine monitoring must include the following information:

- Number of participants recruited, consented, and who have completed data collection
- Percentage of subjects who have declined participation
- Unanticipated challenges and how they were mitigated/addressed
- Study personnel changes
- Proposed changes to the protocol

Additional information and/or interim research updates within the one-year period may be required, and their need is determined at the discretion of the RAT/PB Chair.

3.2 Protocol changes

If study investigators wish to alter the protocol in any way that impacts recruitment, retention, or potential participant risks or benefits, the changes must **first** be approved by the RAT/PB Chair or his/her designate. Protocol changes that do not alter recruitment, retention, risks, or benefits require prompt written notification to the RAT/PB Chair. This correspondence must include proposed change, rationale, and the effective date.

3.3 Protocol violations

In the event that a protocol violation occurs that increases risk and/or decreases benefit to participants, or affects subjects' rights, safety, welfare, or the integrity of the data, the RAT/PB must be notified promptly (within 3 to 5 days of the discovery of the violation). Examples of reportable protocol violations include the following:

- Failure to obtain valid informed consent (e.g. obtaining informed consent on a non IRB-stamped or outdated form)
- Loss of a laptop computer containing identifiable, private information about subjects
- Accidental distribution of incorrect study medication or dosage
- Not following inclusion/exclusion criteria

Protocol violation notification must be written, and must include a description of the precipitating event, possible risk, and measures to remedy the risk.

3.4 Adverse events

In the case of an adverse event that results in harm to a study participant, such as a serious medical complication, the RAT/PB must be notified immediately (within 24 to 48 hours of the event). The RAT/PB may decide to terminate the project, seek outside consultation, more closely monitor the project, or seek out any other appropriate response measures. Notifications of adverse events must be reported directly to the RAT/PB Chair or his/her designate no later than 48 hours after the incident. Communication must be BOTH verbal and written. Written documentation must include a description of the adverse event, harmful consequences, actions taken to eliminate or reduce harm, and a future adverse event prevention plan.

4. Research record maintenance

4.1 Guidelines

HBFF strongly respects and protects patient confidentiality. To this end, all staff members, suppliers, consultants, and visitors **must** sign a Research Confidentiality Agreement, Supplier and Visitor Confidentiality Agreement, or Consultation Confidentiality Agreement (whichever is appropriate for the requested information access) before receiving any access to patient medical or research records. Blank copies of both agreement forms are included in Appendix C.

For any research records that are published (or intended for publication), all research documents will be stored for seven (7) years from the date of publication (or, if no date of publication is available, from the date of protocol closure approval by the IRB). This time frame is consistent with the HBFF's policy for medical records. Records may be kept in either paper or electronic format. Paper records must be kept in a locked file cabinet, while electronic records

should be stored in a limited-access drive and/or be password-protected. Any identifying patient information, including patient names or history numbers, should be removed from project materials before storage.

4.2 Transporting records among HBFF sites

For projects that require researchers to work at multiple HBFF locations, records may need to be transported between treatment center sites. For example, data collected at the Springbrook location may need to be stored at the BCR in Center City. In such cases, records should be transported by either 1) HBFF transportation services, 2) a courier service, or 3) FedEx or a comparable private parcel delivery service.

HBFF employees do not routinely transport patient medical or research records across sites. In the case that a HBFF employee must transport records, they must first be void of all patient identifying information, and the employee must transport the records **directly** to the other site. The preferred method for employee transfer of research records or materials is via the interoffice mail system.

4.3 Shared records

For projects involving collaboration among researchers, HBFF staff members will protect the confidentiality of participants by excluding identifying information as much as possible. This includes, but is not limited to, denying requests for participants' names or substituting novel research identification numbers for medical records or social security numbers. Staff members will create study identification numbers that correspond to identifying information for research data that leaves the organization. Per section 46.114 of 45 CFR 46, if collaborating investigators are from different sites, each site is required to maintain responsibility for safeguarding the rights and welfare of participants. If sites make arrangements for a single IRB review (via one of their own internal IRBs or an external, third-party IRB), this should be documented and a copy should be provided to the RAT/PB. Ownership of shared data will be determined prior to participant enrollment (see section 5.2).

4.4 Use of patient history numbers on research documents

Any research or evaluation documents that will leave the HBFF system for analysis or data entry must be void of all patient/participant identifying information, including history or medical record numbers. In the case of follow-up interviews or other contracted research in which identifying information is necessary, participants must be notified during the informed consent process of what information will be stored, why it will be stored, and how it will be protected. It is recommended that in the case of follow-up data collection, or other research requiring identifying information, researchers use randomly-assigned identification numbers, with a secure master document linking identifiers with patient/participant information accessible only to the principal investigator.

5. Research collaboration

5.1 Definition

The BCR routinely partners with scientists at universities and research organizations to conduct alcohol and drug treatment research. These partnerships range from a HBFF site granting

access to patients for study recruitment to the sharing of study design, data collection and analysis, and presentation or publication responsibilities. To facilitate cooperative productive relationships, BCR requires that researchers at other organizations and HBFF researchers sign a collaboration agreement before enrolling participants in a study.

5.2 Collaboration agreements

Any scientist or student who wishes to conduct research using HBFF resources, such as patient records, patients, or staff members, must first agree to the following conditions (a blank Researcher Collaboration Agreement form is included in Appendix C):

Defined roles

The research protocol must include defined roles. Depending on the complexity of the study, researchers must decide who will be: principal investigator, project/site coordinator, research assistant, medical management, and clinical advisor. The principal investigator is responsible for communication with the RAT/PB and/or IRB, developing study methodology, providing study oversight, data analysis and manuscript preparation. The project and site coordinators facilitate collection of data and communicate with the principal investigator about any protocol questions. Research assistants are responsible for study recruitment, participant tracking, and data collection. For studies with medical interventions, the medical manager prescribes the intervention and oversees any related complications. The clinical advisor is the clinical director of the site. He or she guides the research integration process, when necessary. This may include informing clinical staff members of the project or informing research staff members of any clinical challenges resulting from the study.

Confidentiality

All researchers must sign a confidentiality agreement and maintain confidentiality of patients and patient information (including all verbal and written communications) encountered during the course of conducting research. A blank Research Confidentiality Agreement is included in Appendix C.

Professionalism

In order to ensure the utility of the research results and enhance the relationship between HBFF and the research community, the research must be conducted with scientific integrity and in accordance with professional standards for research. Throughout the process of data collection, data analysis, and presentation of study results, the researcher must maintain an objective view of the research questions and should seek to establish positive relationships with program staff.

Protection of participants

Researchers must provide each subject with the following information to ensure that subjects are able to provide informed consent for participation: a statement that the study involves research, a full explanation of the procedures to be followed, the expected duration of the subject's involvement, a description of the potential discomforts and risks, a statement describing how confidentiality will be maintained, a statement that participation is voluntary and participants have the right to withdraw their consent and discontinue participation at any time without jeopardizing their relationship with HBFF, and the name of a person the subject may contact if they have questions about the research or their rights as a human subject. Each

participant must sign a consent form that indicates his or her willingness to participate in the project. Participation by children under the age of 18 also requires that the child's parent or legal guardian provide written consent for the child to participate in the study.

Upon completion of the research procedures, the principal investigator must attempt to remove any confusion, misinformation, stress, physical discomfort, or other harmful consequences that may have arisen with respect to the participants as a result of the procedure.

Authorship

In accordance with American Psychological Association guidelines, authorship credit is given only to those who actually performed or contributed to the work. Principal authorship may include generating the hypothesis, designing methodology, oversight of data collection, data analysis, and writing the article for publication.

In accordance with the American Psychological Association's ethical guidelines, HBFF reserves the right of first authorship for research resulting from a student dissertation for which he or she completed the majority of the study design, data collection, and analysis. Other student projects do not receive the same protection.

Dissemination of results

Upon completion of the research study, the researcher is responsible for communicating the purpose, nature, outcome and possible practical or theoretical implications of the research to program staff in a manner they can understand. Researchers must provide HBFF with at least one written copy of a summary of research findings before the stated deadline for project completion. HBFF retains the right to determine how the Foundation's name will be used in any published papers. Prior to submission for publication, researchers must provide HBFF with a copy of the submitted manuscript and indicate the journal(s) to which it will be submitted. Submission to any publication other than professional, refereed journals must receive prior approval from HBFF. HBFF retains the right to distribute copies of research findings for educational purposes.

The BCR follows the Englefinger rule, which states that previous publication, such as in the popular press or a scholarly journal, disqualifies research findings from additional/future publication. This means that research intended for journal publication must not be first published in another venue.

Ownership of data

HBFF owns data collected by HBFF staff members about HBFF patients. The Foundation also owns research done in collaboration with other organizations, but collected by HBFF employees. This does not mean that HBFF employees have exclusive rights to publish the data. Rather, after data collection is completed, data will be stored at HBFF, either electronically or as paper files. For projects conducted primarily by outside researchers, HBFF prefers that paper and electronic records be stored at HBFF after data analysis is completed at a HBFF site.

Students and faculty advisers

Students completing research as a part of an undergraduate or graduate course or degree requirement are required to sign the Researcher Collaboration Agreement and a Research

Confidentiality Agreement (see Appendix C). The RAT/PB chairperson or designate and student must agree to the same conditions as non-student researchers. HBFF will provide data entry if the project is completed under the auspices of an existing HBFF research project. Students are required to complete data entry if the project is beyond the scope of current HBFF research. The student's faculty advisor is responsible for advising the student in data analysis and the resulting paper or presentation. If the student and/or faculty member desire to publish the study results, they are held to the same requirements as non-student researchers. This means the paper or presentation must be reviewed by the RAT/PB chairperson before submitted for publication.

6. Relationships with funders

The BCR has two funding sources: HBFF's internal budget and grants or donations from outside sources. The HBFF funds routine treatment outcomes evaluation and research. Topics of research funded by external grants and donations are dependent on the agreed-upon areas of focus determined by the investigator and the funder.

6.1 Hazelden Betty Ford Foundation development

The Development Department and the BCR partner together to raise money for research projects. These include small grants for minor studies or projects (such as the evaluation of an existing program or the creation of a research update) up to large endowments (such as the Huss Family Older Adults and Addiction Research Chair gift). For all gifts to research, development and research staff members work together to solicit the gift and then continue communication as desired by the funder. This communication may include verbal updates or the creation of a more formal report.

6.2 Government agencies

To date, the BCR has obtained small grants from government organizations for research-related activities. For example, the Older Adults and Addiction Research Symposium received a grant from the Substance Abuse and Mental Health Administration to create a video of the presentations. This grant was obtained in partnership with the Development Department.

It is the intent of the BCR to obtain large grants for original (non-routine) patient-based clinical research in the future from the National Institute of Health. The award of a highly competitive National Institute on Alcohol Abuse and Alcoholism or National Institute on Drug Abuse grant would require the creation of an NIH-approved Institutional Review Board at HBFF, developed in accordance with the guidelines and regulations presented in 45 CFR 46. The BCR already has obtained federal approval for a federalwide assurances document (FWA), and currently maintains approval on the document, as needed.

Appendix A: Belmont Report

The Belmont Report

Office of the Secretary

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

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
*** *David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
****Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*
*** *Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

****Deceased.*

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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

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Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance

the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the

case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was

condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common

understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also

requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is

properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be

extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain

groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

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(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Appendix B: Code of Federal Regulations Title 45, Public Welfare, Department of Health and Human Services, Part 46, Protection of Human Subjects (45 CFR 46, “The Common Rule”)

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

Department of Health and Human Services

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

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

Sec.

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

Sec.

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

Sec.

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

Sec.

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

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SUBPART E — Registration of Institutional Review Boards

Sec.

Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

SUBPART A
Basic HHS Policy for Protection of Human Research Subjects

Authority: 5 U.S.C. 301; 42 U.S.C. 289; 42 U.S.C. 300v-1(b).

Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

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

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

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

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

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

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

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

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

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

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

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

§46.102 Definitions.

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

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

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

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

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context

in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

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

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

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

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

[1]Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

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

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1)A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101(b) or (i).

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

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

(4)Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5)Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

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

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

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

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

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

§§46.104--46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

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

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and, to the extent required by, §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§46.109 IRB review of research.

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

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

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

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

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

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

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

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

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

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

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

§46.111 Criteria for IRB approval of research.

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

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

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

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

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

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

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

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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

§46.114 Cooperative research.

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

§46.115 IRB records.

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

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

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

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

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

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

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

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

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

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

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

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

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

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

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

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

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit 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) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

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

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

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

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

§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

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

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

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

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

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

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

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

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

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

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

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

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

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

§46.124 Conditions.

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

Subpart B

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

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

§46.201 To what do these regulations apply?

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

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

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

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

§46.202 Definitions.

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

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

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

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

(d) Neonate means a newborn.

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

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

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

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

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

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

§46.204 Research involving pregnant women or fetuses.

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

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

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

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

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

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

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

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

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

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

§46.205 Research involving neonates.

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

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

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

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

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

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

(1) The IRB determines that:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) The IRB finds that the research presents

a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

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

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

(2) The following:

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

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

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

Subpart C

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

Source: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

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

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

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

§46.302 Purpose.

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

§46.303 Definitions.

As used in this subpart:

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

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

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

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

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

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

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

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

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8366, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

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

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

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

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secre-

tary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

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

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

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

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

Subpart D

Additional Protections for Children Involved as Subjects in Research

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

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101 (b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.

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

§46.402 Definitions.

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

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

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

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

(d) *Parent* means a child's biological or adoptive parent.

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

§46.403 IRB duties.

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

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

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

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

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

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

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

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

(a) The risk represents a minor increase over minimal risk;

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

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

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

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

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

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

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

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

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

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

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

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

§46.409 Wards.

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

(1) Related to their status as wards; or

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

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

Subpart E

Registration of Institutional Review Boards

Source: 74 FR 2399, January 15, 2009, unless otherwise noted.

§46.501 What IRBs must be registered?

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

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

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

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

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

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

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

(e)(1) The approximate numbers of:

(i) All active protocols; and

(ii) Active protocols conducted or supported by HHS.

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

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

§46.503 When must an IRB be registered?

An IRB must be registered before it can be designated under an assurance approved for federalwide use by OHRP under §46.103(a).

IRB registration becomes effective when reviewed and accepted by OHRP.

The registration will be effective for 3 years.

§46.504 How must an IRB be registered?

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

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

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

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

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

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

Appendix C: Hazelden Betty Ford Foundation and Butler Center for Research Forms

Hazelden Betty Ford Foundation

Butler Center for Research
RESEARCH ACTION TEAM AND PRIVACY BOARD RESEARCH REQUEST AND SUBMISSION GUIDELINES

Thank you for your interest in working with the Hazelden Betty Ford Foundation!

In order to use any patient data or information from the Hazelden Betty Ford Foundation (HBFF), or to collaborate on a research project with HBFF staff, principal investigators must submit a proposal including the following items. Please use this form, and keep it under 3 pages to expedite the review process. You can also append any additional information you like. **Important: This review process does not constitute Institutional Review Board (IRB) approval, and documentation of IRB approval will be required for final proposal approval by the Research Action Team and Privacy Board (RAT/PB).**

Background Information

Title of Research Project: *What is the name of your proposal?*

Briefly describe your research topic and its value: *This section should clearly explain the basis for your research questions and/or hypotheses.*

Briefly describe prior research on this topic and how your study will advance knowledge in the research area: *Include a brief literature review that supports your rationale for conducting this research. Describe any preliminary studies and findings that led you to develop this research, and confirm that you are not duplicating any previous efforts. This section should provide rationale for your study design and variables. Be sure to include citations (they can be included as an appendix to save space on this document).*

How will you protect HBFF patient confidentiality? *Guidelines for protecting patient confidentiality should be based on federal regulations for human subjects' protection (45 CFR 46). Information on HBFF policies regarding patient confidentiality can be found in the BCR Research Policy Manual (sections 4.4 and 5.2).*

What is your funding source and approximate budget? *An overall project budget is sufficient – no need for detailed information here.*

How will your findings be disseminated? *Include brief description of HBFF dissemination plan required in the Researcher Collaboration Agreement (detailed in the BCR Policy Manual, section 5.2 "Dissemination of results").*

Please describe your research experience and capability (if you are a student, who is your research advisor?): *Include degrees, certifications, past research experience, and other qualifications for this research. Information for the principal investigator must be included; information for other key research personnel is optional.*

Description of Research Methods to Be Used

Briefly describe the study design: *State the type of research design in one to two sentences. A list of research design definitions is available from the Department of Health and Human Services IRB Guidebook at* http://www.hhs.gov/ohrp/archive/irb/irb_chapter4.htm

Hazelden Betty Ford Foundation

What is your desired sample size? *Include number of subjects, and any a priori power analyses conducted to estimate necessary sample size for statistical significance.*

Briefly describe your planned sampling procedures: *Include pertinent sample demographics and explain how the sample will be selected to accurately reflect the population under study.*

How will data be collected, and who will collect it? *Briefly list what variables will be collected, how they will be collected (electronically, pen and paper, etc.), and which members will be collecting it (roles or specific members). Briefly explain how the integrity of the data will be monitored/maintained during data collection procedures. If specific members of the study team are listed, make sure they are also included on the Study Team Roster submitted with this proposal.*

How much time will it take each patient to participate in this project? *Remember to include time required for study briefing, consenting, and debriefing (if necessary).*

Submission Document Checklist

- ☐ Study proposal
- ☐ Sample consent form
- ☐ Any data collection instruments to be used (questionnaires, tests, etc.)
- ☐ Research Confidentiality Agreement (for all members of the study team)
- ☐ Study Team Roster (can use the BCR Study Team Roster form, or use study team list from study protocol)

All proposals and submission documents should be sent electronically to Dr. Bethany Ranes, RAT/PB Chairperson, at BRanes@hazeldenbettyford.org. Additionally, proposals and submission documents can be mailed to:

Bethany Ranes, Ph.D.
RAT/PB Chairperson
Butler Center for Research
Hazelden Betty Ford Foundation
P.O. Box 11
Center City, MN 55012

NOTE: Upon RAT/PB approval of the research proposal, the principal investigator will be asked to sign a Researcher Collaboration Agreement and/or a Data Use Agreement before any research procedures can begin.

Hazelden Betty Ford Foundation

Butler Center for Research
RESEARCH CONFIDENTIALITY AGREEMENT

I certify that I have been authorized by the Hazelden Betty Ford Foundation (HBFF) Research Action Team and Privacy Board (RAT/PB) to conduct research using patient medical records. I am aware of and agree to the following:

1. Only those patient records and portions of the records pertinent to the research project will be reviewed.

2. Unless otherwise authorized, patient medical records will be viewed on-site at HBFF in a pre-arranged location. Records are to be maintained in a locked cabinet or room, and returned to the pre-arranged location each day.

3. Patient identifying information will not be taken off-site or used in any research papers or reports prepared by the researcher. Patients identifying information includes but is not limited to patient name or location and patient history number.

4. I will not in any way or form disclose patient identifying information to anyone other than back to the program from with the information was obtained. I am aware that drug and alcohol patient records and information are protected by federal law (42 CFR Part 2). Violation of confidentiality (including, but not limited to, disclosing the presence of a patient within the facility) is subject to a fine of $500 in the case of a first offense and fines of up to $5000 for each subsequent offense.

This agreement is in effect for the duration of the research project, and the requirements for maintaining confidentiality of patient information remain in effect beyond the close of the research project.

_____ _____
Signature of Researcher Date

_____
Researcher Name (please print)

_____
Researcher Organization/Institution (please print)

_____ _____
Signature of RAT/PB Chairperson Date

Hazelden Betty Ford Foundation

Butler Center for Research
CONSULTANT CONFIDENTIALITY AGREEMENT

I certify that I have been authorized by the Hazelden Betty Ford Foundation (HBFF) to <<*insert specific purpose of consultation here*>>, and may include a tour/physical review of the HBFF system.

I am aware of and agree to the following:

1. Only information pertinent to the consultation project/contract will be reviewed.

2. Access of any sensitive information will be only with the direct assistance a HBFF staff member.

3. I will not in any way or form disclose patient identifying information to anyone. This includes (but is not limited to) patient's name, occupational affiliation, and history number.

4. I am aware that drug and alcohol patient records and information are protected by federal law (42 CFR Part 2). Violation of confidentiality (including, but not limited to, disclosing the presence of a patient within the facility) is subject to a fine of $500 in the case of a first offense and fines of up to $5000 for each subsequent offense.

This agreement is in effect for the duration of the consultation project/contract, and the requirements for maintaining confidentiality of patient information remain in effect beyond the close of the consulting project/contract.

_____ _____
Signature of Consultant Date

_____
Consultant Name (please print)

_____
Consultant Organization/Institution (please print)

_____ _____
Signature of RAT/PB Chairperson Date

Hazelden Betty Ford Foundation

CONFIDENTIALITY AGREEMENT FOR FOUNDATION SUPPLIERS AND VISITORS

The Hazelden Betty Ford Foundation (HBFF) is committed to protecting the privacy of people who participate in HBFF programs, and abides by all applicable federal and state laws that protect such confidentiality. These standards apply to all persons throughout the organization, including suppliers and visitors.

Basic to the Federal Confidentiality of Alcohol and Drug Abuse Patient Records Regulations (42 CFR Part 2) is that a person's mere presence in the program is a confidential matter. What happens to the patient during his/her time of participation in the program is protected as well. Disclosure of even a patient's presence in the facility is a violation of federal law and can subject the HBFF program and/or individual persons violating the law to fines of up to $5,000.

I understand that I am obligated, at all times, to maintain the confidentiality and privacy of any HBFF patients that I may encounter or observe, and I will not disclose a patient's participation even after discharge from the program. I will not divulge the identity of any patient, or any information regarding any patient, to anyone. If I am questioned about the presence of a patient either past, present or future, my reply must be "I can neither confirm nor deny."

I have read and understand this agreement and understand who this law pertains to HBFF, myself and/or any employees under my supervision. I understand that violation of a patient's right to confidentiality at HBFF is a violation of Federal Confidentiality Regulations, and I am aware of the consequences of such violation.

Signature: _____ Date: _____

Name (Please Print): _____

Name of Organization: _____

Hazelden Betty Ford Foundation

Butler Center for Research
STUDY TEAM ROSTER

Prior to approving any research projects requesting patient information from the Hazelden Betty Ford Foundation (HBFF), the Research Action Team and Privacy Board (RAT/PB) requires documentation of defined research roles for all members of the research team. For a list and definition of some common research roles, please see the BCR Research Policy Manual, section 5.2, "Defined roles". Investigators may use this form to document team members and roles, or they may instead submit the team member roster from their research protocol, as long as the required information from this form is included. An example has been included below for reference (this should be removed prior to proposal submission).

Team Member Name and Degree(s)	Team Member Defined Role for the Study	Team Member Responsibilities
Bethany Ranes, Ph.D.	*Principal Investigator*	*Ongoing communication with the RAT/PB and IRB, developing study methodology, providing study oversight, data analysis and manuscript preparation*

Hazelden Betty Ford Foundation

Butler Center for Research
RESEARCHER COLLABORATION AGREEMENT

Prior to beginning data collection, the RAT/PB Chairperson will review these guidelines with the researcher. The researcher will then be asked to sign a copy of these guidelines indicating that s/he understands and agrees to comply with these guidelines at all times. If the principal researcher is a student, his/her academic advisor will be asked to sign a copy of the guidelines as well. Research conducted in a manner which is inconsistent with these guidelines may result in suspension or termination of project approval.

1) The research protocol must include defined roles for each member of the study team. A Study Team Roster Form must be included with the research proposal (investigators may substitute a list of study team members and their roles from the protocol in lieu of the Study Team Roster Form). For a list of defined roles and a sample list of their responsibilities, please see the BCR Research Policy Manual, section 5.2, "Defined roles".

2) All members of the study team must maintain confidentiality of patients and patient information encountered during the course of conducting research (including all verbal and written communication with patients). A signed Research Confidentiality Agreement for all members of the study team must be included with the research proposal.

3) In order to ensure the utility of the research results and enhance the relationship between HBFF and the research community, the research must be conducted with scientific integrity and in accordance with professional standards for research. Throughout the process of data collection, data analysis, and presentation of study results, the researcher must maintain an objective view of the research questions and should seek to establish positive relationships with program staff.

4) Researchers must provide each subject with the following information to ensure that subjects are able to provide informed consent for participation: 1) a statement that the study involves research, 2) a full explanation of the procedures to be followed, 3) the expected duration of the subject's involvement, 4) a description of the potential discomforts and risks, 5) a statement describing how confidentiality will be maintained, 6) a statement that participation is voluntary and participants have the right to withdraw their consent and discontinue participation at any time without jeopardizing their relationship with HBFF, and 7) the name of a person the subject may contact if they have questions about the research or their rights as a human subject. Each participant must sign a consent form that indicates his or her willingness to participate in the project. Participation by children under the age of 18 also requires that the child's parent or legal guardian provide written consent for the child to participate in the study. Upon completion of the research procedures, the principal investigator must attempt to remove any confusion, misinformation, stress, physical discomfort, or other harmful consequences that may have arisen with respect to the participants as a result of the procedure.

5) Researchers must agree to HBFF policies regarding authorship (please see the BCR Research Policy Manual, section 5.2, "Authorship").

6) Upon completion of the research study, the researcher is responsible for communicating the purpose, nature, outcome and possible practical or theoretical implications of the research to program staff in a manner they can understand. Researchers must provide HBFF with at least one written copy of a summary of research findings before the stated deadline for project completion. For more information on dissemination of study results, please see the BCR Research Policy Manual, section 5.2, "Dissemination of results".

7) HBFF owns data collected by HBFF staff members about HBFF patients. The Foundation also owns research done in collaboration with other organizations, but collected by HBFF employees. This does

not mean that HBFF employees have exclusive rights to publish the data. Rather, after data collection is completed, data will be stored at HBFF, either electronically or as paper files. For projects conducted primarily by outside researchers, HBFF prefers that paper and electronic records be stored at HBFF after data analysis is completed at a HBFF site.

8) Students completing research as a part of an undergraduate or graduate course or degree requirement are required to agree to the same conditions as non-student researchers. HBFF will provide data entry if the project is completed under the auspices of an existing HBFF research project. Students are required to complete data entry if the project is beyond the scope of current HBFF research. The student's faculty advisor is responsible for advising the student in data analysis and the resulting paper or presentation. If the student and/or faculty member desire to publish the study results, they are held to the same requirements as non-student researchers.

9) Researchers must conduct research according to stated purpose and procedures as described in the approved proposal. Any major variance from approved research protocol or issues to be studied must have prior approval of HBFF.

10) Researchers should maintain regular communication with the RAT/PB regarding progress on the project and should notify the Chairperson of any major anticipated delays in completing the project by the proposed deadline.

11) HBFF retains the right to determine how the Foundation's name will be used in any published papers. Prior to submission for publication researcher must provide HBFF with a copy of the submitted manuscript and indicate the journal(s) to which it will be submitted. Submission to any publication other than professional, refereed journals must receive prior approval from HBFF. HBFF retains the rights to distribute copies of research findings for educational purposes.

The signature of the research (and advisor where applicable) indicates that the researcher understands these guidelines and agrees to follow these guidelines at all times. Research conducted in a manner inconsistent with these guidelines may result in suspension and/or termination of project approval.

_____ _____
Signature of Researcher Date

_____ _____
Signature of Academic Advisor (when applicable) Date

_____ _____
Signature of RAT/PB Chairperson Date

Hazelden Betty Ford Foundation

Butler Center for Research
DATA USE AGREEMENT

Identification of limited data set subject to the Data Use Agreement: *Insert name of data set or a brief description of the data to be included in this agreement*

Pursuant to 42 CFR 164.514(e) of the Privacy Rule, this Data Use Agreement is being entered into between the Hazelden Betty Ford Foundation (covered entity, "HBFF") and *Insert name of investigator requesting data set* (recipient of limited data set, "Recipient") as of this *Date* day of *Month*, 20 *Year*.

This limited data set is being disclosed to Recipient by HBFF for the sole purpose of research, public health, or health care operations.

The following individuals and/or job classifications are permitted to use or receive the limited data set:

Name or role of study team member(s) who may access the data
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On behalf of the employees, volunteers, and agents, including subcontractors of Recipient who have access to the limited data set, Recipient agrees to the following terms:

A. Recipient will not use or further disclose the information other than permitted by this agreement or as otherwise required by law;
B. Recipient will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this agreement;
C. Recipient will report any use or disclosure of the information not provided for by this data use agreement to HBFF immediately after the unauthorized use or disclosure is discovered;
D. Recipient will not identify the information contained in the limited data set nor attempt to contact the individuals; and
E. Recipient hereby ensures that any agents, including a subcontractor, to whom the limited data set is disclosed agrees to the same restrictions and conditions that apply to Recipient with respect to such information; and

Recipient acknowledges that HBFF is under legal obligation to report known violations of this Data Use Agreement to the Secretary of the United States Department of Health and Human Services if HBFF is aware of a pattern of activity or practice of the Recipient that constitutes a material breach or violation of this Data Use Agreement unless Recipient and/or HBFF are able to take reasonable steps to cure the breach and/or end the violation.

My signature below indicates my agreement to the above terms, on behalf of Recipient.

_____ _____
Signature Date

_____
Printed Name

_____
Title

Hazelden Betty Ford Foundation

For:

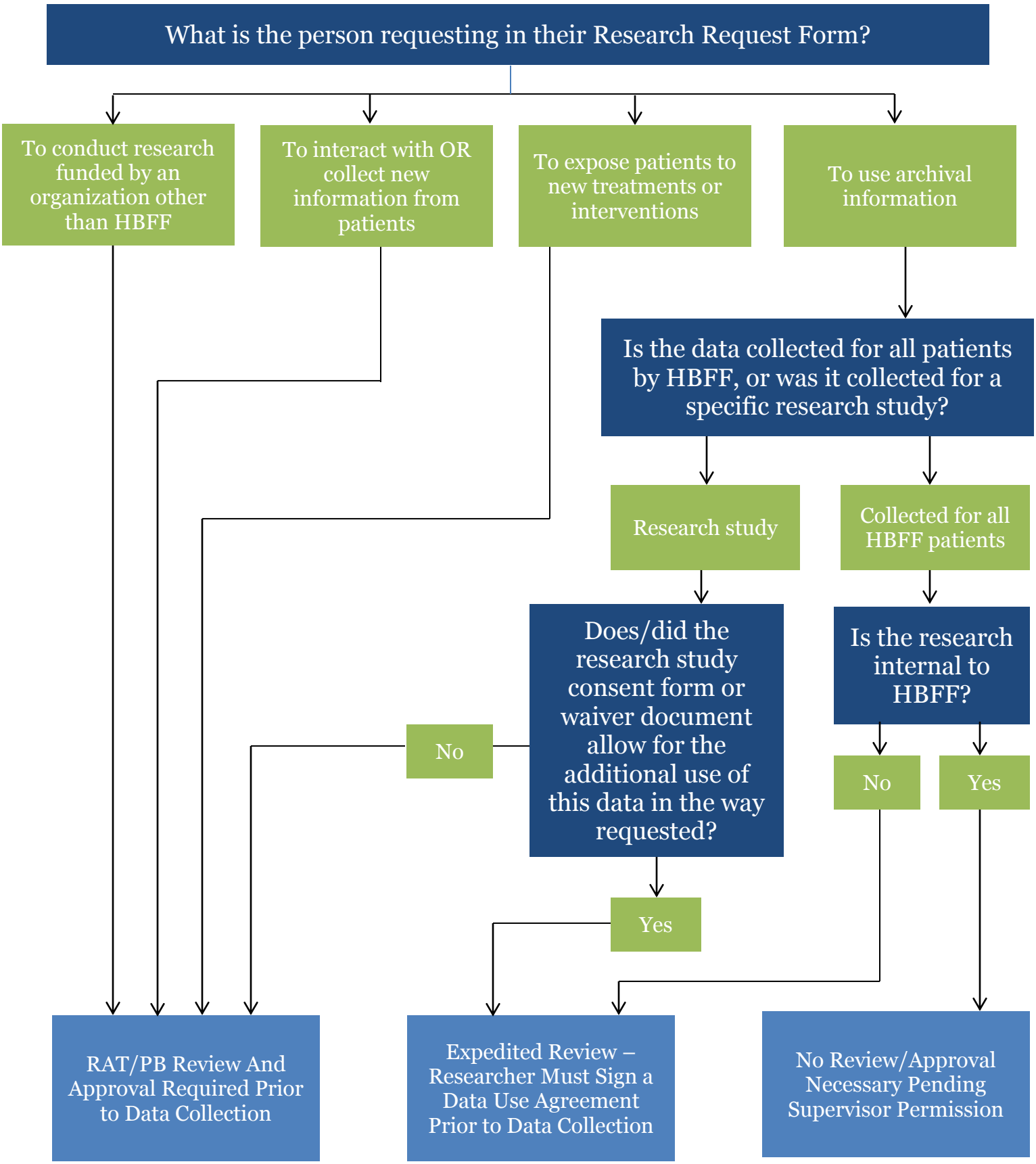
_____ _____
Signature of HBFF staff person Date

_____
Printed Name

_____
Title

Hazelden Betty Ford Foundation

Research Action Team and Privacy Board Review Level Matrix



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