CDC Procedures for Protection of Human Research Participants

October 1997

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC PROCEDURES FOR PROTECTION OF HUMAN RESEARCH PARTICIPANTS

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PROTECTION OF HUMAN RESEARCH PARTICIPANTS
10/1/97[1]

This manual of procedures applies to all research involving human participants conducted by the Centers for Disease Control and Prevention (CDC)[2] or funded in whole or in part by CDC. (1) This includes research conducted by CDC employees, either directly through grants, cooperative agreements or contracts, or in collaboration with outside parties. (2) It also includes research conducted or funded by CDC outside the United States.

Assurance

The Office for Protection from Research Risks (OPRR), National Institutes of Health, is responsible for overseeing the implementation of the Federal Policy (Common Rule for protecting human subjects) throughout the Department of Health and Human Services (DHHS). CDC has provided written assurance to OPRR that it will comply with this policy codified at Title 45, Code of Federal Regulations, Part 46. CDC's Multiple Project Assurance (MPA) contains a detailed description of applicability, principles, CDC policy, responsibilities of CDC staff, and Institutional Review Board (IRB) structure, membership requirements, authorities and responsibilities, and procedures.

Institutional Responsibilities

Office of the Director

No research activity involving human participants unless specifically exempt under 45 CFR 46 or waived by the Secretary, DHHS shall be supported by CDC until the requirements of 45 CFR 46 have been met. The responsibility for the determination that all such requirements are met and that the rights and welfare of human participants have been and will be adequately protected resides at all levels of institutional review. However, the final determination lies with the Deputy Associate Director for Science.

The Deputy Associate Director for Science is the authorized individual to act on behalf of the CDC Director and Associate Director for Science and assumes the obligations imposed by 45 CFR 46 regarding any research involving human participants.

Additional responsibilities of the Deputy Associate Director for Science include the following:

a. Interprets 45 CFR 46 and works with IRBs, CDC researchers and

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[1]This manual will be updated annually.

[2]References to CDC also apply to ATSDR.

Center/Institute/Office (CIO) to formulate and develop CDC policies and procedures consistent with the regulations.

b. Provides written procedures and guidelines for conducting research involving human participants, as needed.

c. Implements CDC's Multiple Project Assurance.

d. Serves as the CDC liaison to OPRR.

e. Convenes regular IRB Chairs meetings. These meetings are attended by IRB Chairs, the Deputy Associate Director for Science, IRB Administrators, and other interested parties.

f. Negotiates and certifies that collaborating institutions have OPRR-approved assurances and IRB approvals.

g. Appoints members to the CDC IRBs and assists CDC IRBs in carrying out their mandate.

Human Subjects Office

Staff within the Human Subjects Office in Atlanta are responsible for carrying out the procedures described in this manual. They include:

a. Coordination of the IRB meetings.

b. Handling of protocols.

c. Handling of expirations and continuations.

d. Coordination of human participants research training and educational opportunities for CDC researchers and IRB members.

At the National Institute for Occupational Safety and Health (NIOSH), responsibilities a-c are handled by the IRB chair; at the National Center for Health Statistics (NCHS) they are handled by the IRB administrator.

Centers, Institute, Offices (CIO)

Each CIO is responsible for designating a Human Subjects Contact. The Human Subjects Contact:

a. Determines and documents whether activities are research or non-research.

b. Determines and documents whether research involves human participants.

c. Determines and documents whether research is exempt from IRB review.

d. Reviews and clears all protocols for IRB review.

e. Serves as the CIO expert and lead on implementing the 45 CFR 46.

f. Works with the Human Subjects Office and investigators, and the IRB chairs, when indicated, to resolve problems.

g. Maintains an internal system for documenting communications between the investigator and the Human Subjects Office for tracking protocols.

Investigators

Investigators are CDC staff who are involved in the design of a research study, development of methods and procedures for the study, collection of data, analysis of data, or interpretation of data. Any CDC staff who is an author on a publication generated from a research study is an investigator of that research study. Investigator's responsibilities are:

a. Makes an initial determination that a proposed study is research involving humans and may need IRB review.

b. Writes protocol and other documentation necessary for IRB review.

c. Is responsible for the conduct of the research.

d. Is responsible for keeping the IRB informed of any relevant changes to an approved protocol.

e. Is responsible for requesting continuation or termination of a protocol.

Institutional Review Boards

CDC has six regular IRBs and two special IRBs. These regular IRBs include one at the NIOSH, two at NCHS -- one regular IRB and one NHANES IRB, and three in Atlanta. The Atlanta based IRBs review and approve research for all other CDC CIOs. CDC/Atlanta has one special IRB which meets on an as needed basis to review protocols that were previously deferred from review and approval. CDC/Atlanta has a rapid assessment IRB which meets on an as needed basis to review research that must be conducted on an emergency basis. Additional IRBs may be constituted as needed.

The primary role of the IRB is to protect the rights and welfare of human beings who are

participants in the research. In accordance with the Federal Regulations (45 CFR 46.111), an IRB may approve research only after it has determined that all of the following requirements are satisfied:

a. Risks to participants are minimized: (i) by using procedures that are consistent with sound research design, and that do not unnecessarily expose participants to risks, and (ii)whenever appropriate, researchers should employ procedures that are being performed on participants for prevention, diagnostic or treatment purposes.

b. Risks to participants are reasonable relative to anticipated benefits, if any, to participants, 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.

c. Selection of participants is equitable. In making this assessment the IRB must take into account the purposes of the research and the setting in which it will be conducted. The IRB must be particularly attentive to the special problems that may arise when research involves vulnerable populations, such as children, pregnant women, fetuses, prisoners, mentally disabled persons, economically or educationally disadvantaged persons. If any of the participants are likely to be susceptible to undue influence or coercion, the IRB may require additional safeguards in the study to protect such participants.

d. Informed consent will be sought from each prospective participant, or the participant's legally authorized representative.

e. Informed consent will be appropriately documented.

f. The research plan makes adequate provisions for ensuring the safety of participants.

g. There are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

<u>Informed Consent</u>

The ethical principle of respect for persons (from the Belmont Report) requires that persons who participate in research shall have the opportunity to choose what shall or shall not happen to them. The IRB must judge whether three conditions are met: disclosure of information (participant has been provided full information regarding the research, comprehension (participant fully understands all ramifications of the research), and voluntariness (participant is

volunteering free of coercion and undue influence).

The IRB will approve protocols that contain the following information as part of the informed consent process (45CFR46.116):

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant'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 participant.

(3) A description of any benefits to the participant 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 participant.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the participant 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 participants' rights, and whom to contact in the event of a research-related injury to the participant.

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

When appropriate, one or more of the following elements of information shall also be provided to each participant:

(1) A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant 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 participant's consent.

(3) Any additional costs to the participant that may result from participation in the research.

(4) The consequences of a participant'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 participant's willingness to continue participation will be provided to the participant.

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

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 requirements to obtain informed consent provided the IRB finds and documents that (45CFR46.116(d)):

(1) The research involves no more than minimal risk to the participants.

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

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

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

All four criteria must be met in order to alter some or all of the consent process.

The informed consent process shall be documented by the use of a written consent form approved by the IRB and signed by the participant or the participant's legally authorized representative. A copy shall be given to the person signing the form. The written consent form may be read to the participant or the participant's legally authorized representative (45CFR46.117), but the investigator shall give the participant or the representative adequate opportunity to read it before it is signed.

A consent form should be written at a level that is understandable to the study population. For most populations, the reading level of the consent form should be at the 8th grade level. Investigators should document to the IRB the reading level of the consent form. If the reading level is at a different level from the 8th grade, justification should be given for the use of the reading level in the consent form.

The investigator may, as an alternative, give the participant or the representative a short written consent form which documents that the elements of the informed consent were presented orally to the participant or representative. The short written consent form is signed by the participant or representative. When this method is used, a witness should observe the oral presentation and a written summary of what is to be said to the participant or representative should be used. The witness should sign the short written consent form and the summary. The person actually

obtaining consent should sign the summary. A copy of the summary should be given to the participant or the representative, in addition to a copy of the short written consent form.

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants under one of two conditions (45CFR46.117 (c)):

1. The only record linking the participant and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern.

2. That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context. In either case, the IRB may require the investigator to provide participants with a written statement regarding the research.

Special Populations

Inclusion of Women and Minorities

CDC IRBs must ensure that women and racial and ethnic minority populations are appropriately represented in research. Women and members of racial and ethnic minority groups should be adequately represented in all CDC research involving human participants, unless a clear and compelling rationale and justification are given that inclusion is inappropriate or clearly not feasible. Although this policy does not apply to studies when the investigator cannot control the race, ethnicity, and gender of participants, women and racial and ethnic minority populations must not be routinely and/or arbitrarily excluded from such investigations.

In addition, women of childbearing potential should also not be routinely and/or arbitrarily excluded from participation even though there are ethical/risk issues to consider for inclusion and exclusion. Information on differences in adverse outcomes or risk profiles for pregnant women may be reason for exclusion. Therefore, pregnancy status may need to be determined prior to enrollment for some studies and, if necessary, during an intervention to safeguard the participants' health. The IRB must determine the degree of certainty of pregnancy status necessary in a study according to the potential risk imposed on the fetus. Requiring a pregnancy test in addition to a woman's self-report of pregnancy status should be dependent upon the degree of risk to the fetus.

Inclusion of women and/or racial and ethnic minority groups in research can be addressed either by including all appropriate groups in one single study or by conducting multiple studies. In general, protocols should employ a design with gender and/or minority representation appropriate to the scientific objectives. It is not a requirement that the study design provide sufficient statistical power to answer the questions posed for men and women and racial and ethnic groups separately; however, whenever there are scientific reasons to anticipate differences between men

and women and/or racial and ethnic groups with regard to the hypothesis under investigation, investigators should include an evaluation of these gender and racial/ethnic group differences in the study proposal. If adequate inclusion of one gender and/or minority group is impossible or inappropriate with respect to the purpose of the proposed study, the rationale for the study population must be well explained and justified. Similarly, if in the only study population available, there is a disproportionate representation of one gender or minority/majority group, the rationale for the study population must be well explained and justified. The cost of inclusion of women and/or racial and ethnic minority groups shall not be a permissible consideration for exclusion from a given study unless data regarding women and/or racial and ethnic minority groups have been or will be obtained through other means that provide data of comparable quality.

Research Involving Prisoners as Participants

In addition to all other IRB responsibilities, any protocol involving prisoners as research participants must also meet specific requirements as described in Subpart C of the Federal Regulations. A prisoner is defined as 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, trials, or sentencing.

The specific requirements are:

> With respect to the IRB, a majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB and at least one member of the IRB 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 IRB only one IRB need satisfy this requirement. Generally, because CDC engages in collaborative research, CDC will depend upon the local site's IRB to have a prisoner representative.

In addition the IRB shall approve such research only if it meets the following requirements (45CFR46.305 and 45CFR46.306):

> (1) The research under review represents one of the following categories:
>
> (a) 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 participants.
>
> (b) 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 participants.

(c) 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). Following approval by the CDC IRB, the Deputy Associate Director for Science will notify OPRR who will provide final approval for the research.

(d) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the participant. In cases in which those studies require the assignment of prisoners to control groups which may not benefit from the research, upon approval by the CDC IRB, the Deputy Associate Director for Science will notify OPRR who will provide final approval for the research.

(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 participants 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 IRB justification in writing for following some other procedures, control participants 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 participant 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 that each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

(7) Where the IRB finds that 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.

Upon approval of the protocol by the IRB, the Deputy Associate Director for Science will notify OPRR about the research, the category under which it is permitted (45CFR46.306) and that the duties of the IRB under 45CFR46.305 have been fulfilled.

Finally, any protocol involving prisoners as research participants must meet all applicable state laws.

Research Involving HIV Antibody Testing

The IRB must assess the potential risk/benefit balance of the study and assure that the consent process clearly distinguishes experimental procedures from clinical care.

When HIV-antibody testing is to be performed as part of a research protocol, both the protocol and the consent form must state that the HIV testing is being performed for purposes of the study; the protocol must include a justification as to why this testing is being performed; pre- and post-test counseling of the participants by qualified personnel must be performed and the participants must be informed of their test results. The participants should be counseled as to the various risks associated with HIV testing as well as the risks associated with being HIV positive. If the person is HIV positive, the various options available for treatment should be discussed; the details of this counseling, where, when and by whom it will be done, should be included in the consent form; the protocol should discuss how the confidentiality of the HIV-antibody test results will be maintained.

In 1988 the Public Health Service issued a policy stating that research participants tested for HIV antibody, if the testing is conducted or supported by Federal funds, must receive their results and be provided with appropriate counseling. There are three exceptions: pertaining to the individual, pertaining to protocol design, and pertaining to foreign sites. In the first exception, where there are compelling and immediate reasons that justify not informing a particular individual that he or she is seropositive, (e.g. an indication that an individual would attempt suicide), the particular individual need not be informed of HIV test results. When this exception is made the principal investigators will promptly report the exception to the local IRB and the CDC IRB without identifying the individual.

The second exception pertaining to protocol designs covers circumstances in which extremely valuable knowledge might be gained from research involving participants who would be expected to refuse to learn their HIV test results. The IRB shall consider the particular circumstances of the research, the characteristics of the target research participants, and other factors, and may approve a testing procedure that would allow research participants to participate without being informed of their individual results. In proposing such an exception, the investigator must demonstrate to the satisfaction of the IRB that (a) research participants will be informed of their risk of infection; (b) research participants will receive risk reduction counseling regardless of whether they receive their test results; (c) there is good reason to believe that a requirement for test results notification would significantly impair collection of study information that could not be obtained by other means; and (d) the risk/benefit ratio to individuals, their partners, and society will be periodically reevaluated by the IRB so that the study might be revised or terminated if it is determined that it is no longer justifiable to allow participants to continue to participate without receiving their HIV test results.

The third exception covers protocols conducted at foreign sites. Activities should be evaluated to account for cultural norms, the health resource capabilities and official health policies of the host country. If a research protocol review is involved, the reviewing IRB must consider whether any modification to the policy is significantly justified by the risk/benefit evaluation of the research. .

The CDC IRB must approve any protocol that falls into exception 2 or 3. If the IRB approves the protocol, the Deputy Associate Director for Science will submit the decision to the Director, CDC. Prior to or at the same time that the decision is being posed to the Director, CDC, it must also be sent to OPRR. In the event that the Director, CDC disagrees with the IRB's decision and will not approve the exception, the IRB will be so informed. The Director, CDC could not, however, approve the exception if the IRB disapproved it.

Research Involving Pregnant Women, Fetuses, and Human *in vitro* Fertilization

In addition to all other IRB responsibilities, for any research involving fetuses, pregnant women, and human in vitro fertilization the IRB shall meet the specific requirements described in Subpart B of the Federal Regulations. Pregnancy encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus. Fetus means the product of conception from the time of implantation until a determination is made, following expulsion or extraction of the fetus, that it is viable (being able, after either spontaneous or induced delivery), to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration.). In vitro fertilization means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

The CDC IRB will, in addition to the other requirements in the Federal Regulations, determine that adequate consideration has been given to the manner in which potential participants will be selected, and adequate provision has been made by the principal investigator for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the IRB or participant advocates in: (i) overseeing the actual process by which individual consents required by this Subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen).

General Limitations Related to This Research

No activity to which this Subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed.

(2) Except where the purpose of the activity is to meet the health needs of the mother or the

particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy, and determining the viability of the fetus at the termination of the pregnancy.

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

Activities Directed Toward Pregnant Women as Participants

No pregnant woman may be involved as a participant in an activity covered by this Subpart unless:

(1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

(2) The risk to the fetus is minimal. Any research protocol permitted under this Subpart may be conducted only if the following requirements are met: the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: the purpose of the activity is to meet the health needs of the mother, his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy resulted from rape.

Activities Directed Toward Fetuses *in utero* as Participants

No fetus in utero may be involved as a participant in any activity covered by this Subpart unless:

(1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

(2) The risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any research protocol permitted under this Subpart may be conducted only if the following requirements are met: the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy

resulted from rape.

Activities Directed Toward Fetuses *Ex Utero*, Including Nonviable Fetuses, as Participants

Until it has been ascertained whether a fetus ex utero is viable, a fetus ex utero may not be involved as a participant in an activity covered by this Subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

No nonviable fetus may be involved as a participant in an activity covered by this Subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

In the event the fetus ex utero is found to be viable, it may be included as a participant in the activity only to the extent permitted by and in accordance with the requirements of other parts of the Regulations.

Any protocol involving pregnant women, fetuses, and in vitro fertilization as research participants must meet all applicable state laws. Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable state or local laws regarding such activities.

Waivers to these requirements may be granted only after approval by the IRB and the Secretary, DHHS.

Research Involving Children as Participants

In addition to all other IRB responsibilities, any protocol involving children must meet specific requirements as described in Subpart D of the Federal Regulations. 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 (46.402(a)) . This definition, when read in the context of the Federal Regulations requires a review of state or local law to determine the age at which an individual can consent to participation in research

without parental consent. 46.402(a) should be interpreted in conjunction with each state's general medical consent laws. The mere existence of laws authorizing minors to consent to specific medical treatments (e.g. treatment of sexually transmitted diseases) should not be broadly interpreted to authorize minors to consent to research regarding that treatment, unless so stated in the law. This interpretation should not unduly restrict otherwise ethical research. IRB's may waive the requirement for parental consent in accordance with the procedures set forth in 46.116 if appropriate measures are taken to protect the interests of minors.

The IRB must consider the benefits, risks, and discomforts of the research and assess their justification for childrens' participation in light of the benefits to the child-participant(s) or to society as a whole. In calculating the risks and benefits, the IRB should consider the circumstances of the participants under study, the magnitude of risks or discomforts that may accrue from research participation and the potential benefits the research may provide to the participant or class of participants.

An important aspect of IRBs' considerations of research involving children is an evaluation of what constitutes "minimal risk." Procedures which generally present no more than minimal risk to healthy children include: urinalyses, small amounts of blood obtained by venipuncture, electroencephalography (EEG), allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However, the assessment of the probability and magnitude of harm or discomfort may be different in ill children and may vary depending on the diseases or conditions that the children may have. For example, obtaining research blood samples from a very ill and anemic child may present more than minimal risk to the child. The IRB must also consider the extent to which research procedures would be a burden to a child-participant, regardless of whether the child is accustomed to the proposed procedures. Procedures that exceed minimal risk may be difficult to define in the abstract, but should not be difficult to identify on a case-by-case basis. Higher risk procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress also may exceed minimal risk.

Additionally, for any research involving children the IRB must verify that the research protocol has made adequate provisions for soliciting the assent of the children and the permission of the parents or legal guardian. Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research. Parent means a child's biological or adoptive parent. Guardian means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

When children are involved in research, the IRB must make provisions for the assent of the children and the permission of the parents. The IRB must determine whether the permission of both parents is required.

Although children are not capable of giving legally valid consent, they may be able to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether they wish to participate in research, particularly if they can comprehend and appreciate what it means to be a volunteer for the benefit of others and the research is not likely to benefit them directly. Taking into account such factors as the nature of the research, and the age, status and medical condition of potential participants, the IRB must determine for each protocol, whether all or some of the children are capable of assenting to participation. There is no requirement that assent be sought at a specific age, but that it be sought when in the judgment of the IRB, the children are capable of providing assent. Generally, CDC IRBs require that assent be obtained from children 7 years and older.

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 participants are capable of assenting, the IRB may still waive the assent requirement under the criteria for waiving consent in 45CFR46.116.

In addition to the criteria for waiving consent in 45CFR46.116, if the IRB determines that a research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), it may waive the usual consent requirements, provided an appropriate mechanism for protecting the children who will participate in the research is substituted, and provided further that the waiver is consistent with Federal, state, and local laws. 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 participants, and their age, maturity, status, and condition.

Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research 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 participants are not wards.

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.

Categories for Research Involving Children

The IRB must classify the research into one of four categories and must document in the minutes their discussions of the risk and benefits of the research study. The IRB may approve research in each of these four categories of research involving children:

1) Research that does not involve greater than minimal risk to children.

The IRB may approve research in this category if adequate provisions are made for obtaining assent of the children and the permission of their parents or guardian. The IRB may decide that the permission of one parent is sufficient for the research to be conducted.

2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual (child) participant.

To approve research in this category, the IRB must determine that the risk is justified by the anticipated benefit to the participants, the relation of the anticipated benefits to the risk is at least as favorable to the participants as that presented by available alternative approaches, and adequate provision is made for obtaining assent of the children and permission of their parents or guardian. The IRB may decide that the permission of one parent is sufficient for the research to be conducted.

3) Research involving greater than minimal risk and no prospect of benefit to the individual (child) participant, but likely to yield generalizable knowledge about the participant's disorder or condition.

To approve this category of research, the IRB must first determine that the risk of the research represents no more than a minor increase over minimal risk; that the intervention or procedure presents experiences to the child-participants that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; the intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition; and adequate provisions are made for obtaining assent of the children and permission of their parents or guardian. The permission of both parents must be obtained 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.

4) Research not otherwise approvable under one of the other three categories but the IRB determines that the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. In these cases upon approval by the CDC IRB, the Deputy Associate Director for Science will notify OPRR who will provide final approval for the research.

Any protocol involving children as research participants must meet all applicable state laws.

Research Involving CDC Employees

Occasionally, there may be circumstances under which an investigator wishes to use CDC employees as research participants.

The protocol must contain the procedures that will be used to assure that participation is voluntary and there is no coercion by supervisors, peers or other groups. To help in this, the investigator must consider obtaining volunteers from units outside the investigator's and his or her supervisor's unit or posting an announcement about the research project and the need for volunteers. The announcement must be included in the protocol. Regardless of what mechanism is used, the consent form must include a provision that emphasizes strongly that the individual's participation is truly voluntary, and the fact that the individual can contact the Human Subjects Office (Atlanta) or the Chair of the IRB (NCHS, NIOSH) to file complaints about possible coercion.

For each protocol that uses CDC employees as research participants, a list of individuals who have participated must be maintained and supplied to the IRB, in case there is a need by the IRB to interview the participants for an investigation of alleged coercion.

The consent form and the protocol must contain all of the conditions under which the CDC employee will participate.

The protocol must contain the procedures utilized to assure that sensitive data remain confidential. The best solution is to have no demographic data collected.

If demographic data are collected, or results are provided to the participant, procedures must be described to minimize the risk of an individual's co-workers identifying participants. One solution might be to have a third party (outside of CDC) do the data collection. This third party would then have the only "cross-file" that would link results with an individual.

The protocol and consent form must contain a statement as to the expected number and duration of time periods that CDC employees will be expected to spend in the study and whether compensation will be offered. The consent form must appropriately cover the liability issues if the individual participates on his or her own time or during his or her regular tour of duty.

Research Involving Non-English Speaking Participants

The IRB should assure that adequate provisions have been made for appropriate translation of the consent document or the availability of translators to ensure an adequate understanding of the research project.

Research participants who do not speak English should be presented with a consent document

written in a language understandable to them. When written documentation is not feasible, oral presentation of informed consent information in conjunction with a short written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally may be used. A witness to the oral presentation is required, and the participant must be given copies of the short written consent document and the summary. When this procedure is used with participants who do not speak English, the oral presentation and the short written consent document should be in a language understandable to the participant; the IRB-approved English language informed consent may serve as the summary; and the witness should be fluent in both English and the language of the participant.

Research Involving Food and Drug Administration (FDA) Regulated Products

Any research study involving products regulated by the FDA, including test articles and investigational new drugs must meet the requirements of 45 CFR 46 and FDA regulations for protecting human subjects, 21 CFR 50 and 21 CFR 56. A test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation by the Food, Drug and Cosmetic Act or under sections 351 or 354 of the Public Health Service Act. An investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation.

Establishment and Composition of CDC's IRBs

Each IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' background, to foster respect for its advice and counsel in safeguarding the rights and welfare of human participants. In addition to possessing the professional competence necessary to review and approve specific research activities, the IRB must be able to ascertain the acceptability of proposed research in light of (1) ethical principles set forth in the Belmont Report, (2) the Federal Regulations, 45CFR46 (3) applicable Federal, state, and local laws, and (4) standards of professional conduct and practice.

IRB members and Chairs are appointed by the CDC Deputy Associate Director for Science for two- to four-year renewable terms, after having been nominated by their CIO Human Subjects Contact. Each CDC IRB shall have a chair, co-chair, and at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Each IRB shall have two people who are not affiliated with CDC and at least one person who is a nonscientist. Major scientific disciplines such as medicine, laboratory sciences, epidemiology, and behavioral and social sciences must be represented on each IRB. Each IRB shall have at least one female member and a proportion of membership representing minorities appropriate to the types of research reviewed.

In Atlanta, a list of alternate IRB members is maintained. Alternate IRB members are assigned to each core IRB member. For example, an alternate IRB member who is a physician is assigned as a potential alternate for core IRB members who are physicians. Alternate members are asked to sit on the IRB when either an additional member is needed to satisfy the quorum requirement or when a specific discipline needs to be represented.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals become ad hoc members and will not vote with the IRB. Changes in IRB membership are reported to the OPRR.

Special IRB

A special IRB has been set up to review cooperative research protocols that have been reviewed by a local IRB but were not reviewed by the CDC IRB. The IRB consists of five people, including one person not affiliated with CDC, and one nonscientist. Three, with at least one being a nonscientist, in attendance is a quorum.

Rapid Assessment Board

This IRB reviews emergency research which is defined generally as research resulting from the sudden onset of a public health threat that requires an immediate response by CDC investigators. Generally, CDC conducts approximately 6 - 8 emergency research studies annually. This IRB consists of five people, including one person not affiliated with CDC, and one nonscientist. Three, with at least one being a nonscientist, in attendance is a quorum.

Conflict of Interest

No IRB may have a member participating in the IRB's initial or continuing review of any protocol in which the member has a conflicting interest, except to provide information requested by the IRB. A conflicting interest is defined as any interest in the research such that a member might not be able to review objectively a protocol for protection of human participants according to the Federal Regulations. Types of interests that may cause a conflict are financial interest, special or unusual knowledge about the research, direct involvement in the research, supervision of any of the research investigators by the member, supervision of the member by the research investigators or personal involvement with the investigators. In addition, any time an IRB member feels uncomfortable about participating in the review of a protocol, that member may have a conflict of interest.

Each IRB member is required to sign a conflict of interest form at the beginning of each IRB meeting stating whether he/she has a conflicting interest with any item on the agenda. These forms are collected and maintained by the Human Subjects Program Specialist (Atlanta), the IRB Administrator (NCHS), or the IRB chair (NIOSH). During the discussion of the agenda item which is of conflict to the member, the member must leave the room and recuse himself or

herself from discussion and the vote on said issue. A quorum of remaining IRB members is required for full board deliberation of the agenda item.

IRB Meetings

The Atlanta based IRBs, convene once every three weeks at a specific CDC facility. The NCHS IRBs meet every other month. The NIOSH IRB meets once a month. Additional meetings are called as needed.

In Atlanta, the Human Subjects Review Specialist in consultation with the IRB chairs is responsible for setting the agenda for each meeting and calling convened meetings as often as required to accomplish the business of the IRB. The Human Subjects Review Specialist places the protocol on the agenda for a designated IRB meeting. The Program Specialist prepares an agenda packet which includes each new protocol, amendment or continuation being reviewed. The packet includes the protocol and the Absence of Conflict of Interest form. At least seven days before the IRB meeting, the packet is sent to each member of the IRB.
At NCHS, the IRB Administrator performs these functions. At NIOSH, the IRB chair sets the agenda, convenes each meeting and handles the Absence of Conflict of Interest form; the Principal Investigator sends protocols to the chair and each member of the IRB.

Meetings are generally closed to non-IRB members. However, investigators may attend to clarify issues at the request of the IRB. Deliberations and voting on protocols is closed. Full board actions require the presence of a quorum of the voting members, defined as a 50% plus one majority of the membership including at least one member who is a non-scientist. If any member recuses himself or herself because of a conflict of interest, a quorum of the remaining members is needed for full board actions.

A primary reviewer system is used to review new protocols, amendments, and requests for continuations. The Human Subjects Program Specialist, or the IRB Administrator, in consultation with the IRB chairs, assigns a new protocol, amendment, or request for continuation to an IRB member for primary review. All IRB members are expected to review all items on the agenda. For new protocols, the primary reviewer is responsible for making a presentation describing the research including any important human participants protection issues. In some cases, the IRB chair may ask the primary reviewer to draft the IRB report, which the chair may require be cleared by him/her. The IRB Chair is ultimately responsible for the IRB report that is sent to the investigator. For amendments and requests for continuation, the primary reviewer is responsible for reviewing the protocol folder in its entirety, and for making a presentation describing the requested change, if an amendment is requested, or describing progress on the study, if it is a request for continuation.

IRB meetings are conducted in accordance with Robert's Rules of Order. That is, at a minimum, the Chair conducts the meetings, there is a predetermined agenda, the minutes of the prior meeting are voted upon, and all actions and resolutions require the voice or show-of-hands vote of the members present following discussion and the making and seconding of a motion.

Minutes from every meeting must include recording: attendees; any action taken; the vote on the 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 controversial issues and their resolution. In Atlanta, the Human Subjects Program Specialist is responsible for taking minutes; at NCHS, the IRB Administrator handles this function; and at NIOSH, it is handled by the IRB chair.

IRB Actions on Research Protocols

An IRB may vote to defer, approve, disapprove, or approve contingent upon a satisfactory response from the principal investigator of the research protocol. A protocol is deferred when the IRB requests substantive clarifications, protocol modifications, or informed consent document revisions. The full board reviews and approves the investigator's response. The IRB may vote to delegate review to the chair only when the protocol requires minor changes which do not require a full board approval.

These actions require the vote of a majority of the members present at the meeting. The Chair does not vote, except to break a tie. If the vote is not unanimous, the minority opinion must be recorded in or attached to the minutes. An IRB member may abstain from voting for any reason, without explanation. A member may change his/her vote until the time the vote is finally announced by the Chair. After that, a member's vote may be changed only by permission of the IRB which may be given by general consent. The IRB requires that issues be addressed satisfactorily before a protocol is approved. Either the Chair of the IRB or the full IRB may certify that the issues have been addressed by the principal investigator. The IRB may also offer nonbinding recommendations with its action to approve a protocol. The IRB report addresses four categories: general issues; protocol issues; consent form issues; and addendum issues. Each category is subdivided as follows: requirements (these requirements must be addressed in order for the protocol to be approved); recommendations (suggestions to improve the clarity and quality of the protocol that require a response); of note (minor comments, typographical errors, grammatical errors, etc).

In Atlanta, the IRB chair sends the report to the Human Subjects Review Specialist. The Human Subjects Review Specialist (Atlanta); the IRB Administrator (NCHS), or the IRB Chair (NIOSH) sends, via registered E-mail and hardcopy via interoffice mail (NIOSH), the IRB report to the principal investigator. The principal investigator submits a written response to the Human Subjects Review Specialist(Atlanta) , IRB administrator(NCHS) or the IRB chair and each member (NIOSH). The chair, and if appropriate, the entire committee review the written response. The IRB votes to approve, approve contingent upon required changes, or disapprove. Upon approval, a written approval letter is sent to the principal investigator. The final revised protocol (with corrections) must be returned by the principal investigator to the Human Subjects Review Specialist (Atlanta), the IRB Administrator (NCHS), or the IRB chair and each IRB member (NIOSH). When a protocol is disapproved, the IRB chair provides to the principal investigator a written notification of this decision and a statement of the reasons for its decision. The principal investigator is allowed to request that the IRB reconsider its decision or to

resubmit the protocol with changes.

Appeal of IRB Actions

By Federal regulation, institutional officials may not approve research that has been disapproved by an IRB. There is no mechanism for an appeal of IRB decisions to other institutional components; the IRB is an autonomous entity with its decisions being binding. Principal investigators may request an IRB to reconsider a decision regarding a research protocol. However, investigators do not have the option to seek the reversal of an IRB decision by submitting the same protocol to another CDC IRB.

Reporting of Adverse Events

Any adverse events including physical, psychological, and social injuries to participants, breaches of privacy or confidentiality, unanticipated problems that are reported to an IND sponsor, and any breach in the protocol must be reported to the IRB. Serious events should be reported immediately to the IRB; other events should be reported in a timely fashion but no later than in the request for continuation or notification of termination. The report should include a statement about the nature of the adverse event, impact on participants, and what has been done to correct the problem. Following review by the IRB, the IRB Chair will notify the Deputy Associate Director for Science who will notify OPRR in writing of the incident and the corrective actions taken.

IRB Records Management

The Human Subjects Office (Atlanta); the IRB Administrator (NCHS), or the IRB chair (NIOSH) maintains copies of protocols and consent documents that each IRB has reviewed including continuing reviews; scientific evaluations, if any, that accompany protocols; minutes of its meetings; a current approved membership list; progress reports submitted by investigators; reports of injuries to participants; copies of all correspondence between the IRB and investigators; statements of significant new findings provided to participants; and documentation of collaborative and cooperative research activities occurring at other institutions with other OPRR-approved assurances, including documentation of protocol and consent form approval by the IRBs at these sites. All records and documents are maintained for at least three years after completion of the research, and the records are accessible for inspection and copying by authorized representatives of OPRR.

Protocol Handling

New Protocols

All research studies, including pilot studies, involving CDC investigators must be reviewed and approved by a CDC IRB before they begin, unless they are exempt from IRB review. Principal investigators write research protocols for submission to the IRB. The principal investigator

develops a protocol. The protocol is reviewed and cleared at the CIO level (division level -- NIOSH) of CDC. Final clearance at this level is the designated human subjects research official for the CIO. The protocol, with CDC form 0.684, *Human Subjects Request for Protocol Approval* and other required forms is sent to the the Human Subjects Office (Atlanta), IRB Administrator (NCHS), or the IRB chair (NIOSH) who logs it into a protocol database. At NIOSH, the principal investigator sends a copy of the protocol to each NIOSH IRB member. A file is created and maintained for every protocol. The file contains the protocol and every accompanying form issued during the life of the protocol. The Human Subjects Review Specialist (Atlanta), IRB Administrator (NCHS), or the IRB Chair (NIOSH) reviews and determines based upon 45CFR46.110, whether the protocol is eligible for review by the expedited review process or whether it requires full board review. Each new research protocol is assigned to an IRB in order of readiness.

Amendments

In conducting the research study, if changes to the protocol, consent form, or other study documents are needed from what was approved by the IRB, the principal investigator submits a description of and justification for the change in the protocol, along with CDC form 0.684 to the IRB through the Human Subjects Office (Atlanta), the IRB administrator (NCHS) or the IRB chair (NIOSH). If it is a minor amendment (e.g., additional sites added; submission of site specific consent forms; revisions of data collection documents that do not add increased sensitivity to originally approved protocol; expansion of study population that does not include inclusion of new categories of participants; addition/deletion of laboratory tests that do not increase the risk or impact the validity of the study) which presents no additional risks to the participant, the review and approval are handled by the expedited review process; anything other than a minor amendment must go to the full IRB for approval.

If significant findings are reported in the literature that may result in a change in the risks or benefits associated with the study or require a change in the protocol, the principal investigator should report the literature findings to the IRB immediately along with recommended corrective actions to the protocol for approval.

Continuation of Protocol Approvals

A research protocol must be reviewed by an IRB until the study is completed. Completion of a study is defined as all data from the study have been analyzed. Approval for a research protocol is valid for no more than one year. IRBs are required by the Federal Regulations to conduct continuing reviews of research at intervals appropriate to the degree of risk, but not less than once a year. The principal investigator is responsible for the timely submission of a continuing review application to the IRB that previously reviewed the protocol. Research protocols that required full IRB review initially and that have not completed participant accrual, generally require full IRB review for continuation; the review must take place at a convened meeting of the IRB and must be approved by a majority of the members present. The IRB's stipulations, if any, must be met by the principal investigator before approval for continuation is granted. At the

time of continuation reapproval, research protocols that required full IRB review initially, have completed participant accrual, and are in the process of analyzing data, may be reviewed using the expedited process. Research protocols that were reviewed using the expedited review process initially may be reviewed using the expedited review process as long as the degree of risk associated with the study has not changed.

To assist principal investigators in submitting continuation requests in a timely fashion, 90 days before protocol expiration, the Human Subjects Program Specialist (Atlanta), the IRB Administrator (NCHS) or the IRB Chair (NIOSH) notifies, via registered E-mail, the principal investigator of the upcoming deadline. The principal investigator is asked to submit the Request for Approval of Continuation of Protocol No Change. A second notice is sent 60 days before expiration, if the Principal Investigator has not responded. If necessary, 30 days before expiration, the Deputy Associate Director for Science, submits, via registered E-mail to the CIO Human Subjects Contact, a request for the status on the protocol and for the principal investigator to complete the form. Requests for continuation must be received by the Human Subjects Office 30 days prior to the expiration date.

A continuation request must include all of the following:

(1) a request for protocol continuation form

(2) a copy of the currently approved informed consent document if participants are being accrued

(3) a brief report on the status of the project including the protocol's progress to date, the reason(s) for continuing the study and plans for the next approval period, a description of any adverse events or unanticipated problems involving risks to participants or others, a discussion of number of refusals, withdrawal of participants from the research or complaints about the research, a summary of any recent literature, findings obtained thus far, modifications to the research since the last review relevant to the study, e.g., the existence of risks different from those previously described, and an expected completion date of the project, and the number of participants by gender and race/ethnicity enrolled in the study.

If changes in the protocol are substantive or there are changes in the consent document, data collection instruments or site locations, an amendment request should be submitted along with the
continuation request.

If the continuation request is not received by the expiration date, the IRB will terminate the approval of protocol. A termination letter is sent to the Human Subjects Contact and the principal investigator with a copy to OPRR. Reactivation of the study requires submission of a new protocol to the IRB.

If the continuation request is received prior to the expiration date, but the IRB approval of the

protocol expires before it is reapproved, the principal investigator and Human Subjects Contact are notified that no new participants can be accrued until the protocol is approved by the IRB. If the continuing review is under active consideration by the IRB, but has not been approved one month after the expiration due, the principal investigator will be notified again that participant accrual is suspended and that unless the continuing review process is completed within 45 days from the date of the reminder, all protocol activities may be suspended or terminated.

The timing of submission of the continuation request does not affect the anniversary date for subsequent reviews, i.e., there is no "resetting the clock" for the next due date, unless the IRB requires an earlier review. Approval dates are set to the anniversary date of the initial IRB approval of the protocol.

Expedited review

The Human Subjects Review Specialist (Atlanta), IRB administrator (NCHS), or the IRB Chair (NIOSH) determines whether a new protocol, amendment, or continuation request is eligible for expedited review. Under an expedited review procedure, the review is carried out by the IRB chair or the chair designee. 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 it is reviewed in accordance with the nonexpedited procedure set forth in 45CFR46.108(b). At every IRB meeting each member is provided a written report of any protocols handled through expedited review since the last regular meeting.

Selected categories of research may be reviewed through an expedited review procedure, if the research involves no more than minimal risk as specified in the Federal Regulations. These categories include:

(1) Collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3) Recording of data from participants 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the participant's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters (5

milliliters equals 1 teaspoon) in an eight-week period and no more often than two times per week, from participants 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate participants' behavior and the research will not involve stress to participants.

(10) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

Suspensions or Terminations

CDC IRBs have authority to suspend or terminate approval of research when it is found that a previously approved research protocol is not being conducted in accordance with the IRB's requirements or that the protocol has been associated with unexpected serious harm to participants. The IRB promptly prepares a statement identifying the reasons for it's action. This statement is reported to the principal investigator and the appropriate institutional officials. If the research is collaborative and conducted under a funded agreement, notification to the awardee will be made by the Grants Management Officer or the Contracting Officer. Suspensions and terminations will be reported to OPRR by the CDC Deputy Associate Director for Science.

Exempt Research

Research may be exempt from IRB review. CDC uses the criteria for exemption as described in 45 CFR 46.101. In Atlanta, the CIO Human Subjects Contacts, at NCHS the IRB administrator or chair and at NIOSH the IRB chair make the determination whether research is exempt. Documentation of the exemption must include the specific category in 45CFR46.101 justifying the exemption. Each exempt research study is reported to the Human Subjects Office and tracked in the protocol tracking system. Exempt research is reviewed on an annual basis to determine whether it continues to meet the criteria for exemption.

Note: The exemption criteria below do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization.

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special education instructional strategies, or 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: information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and any disclosure of human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation.

> **Note**: The above exemption of research involving survey or interview procedures or observation of public behavior, does not apply to research with children except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

(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 if the human participants are elected or appointed public officials or candidates for public office; or 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 participants cannot be identified, directly or through identifiers linked to the participants.

(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: public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or 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, if wholesome foods without additives are consumed or 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.

Cooperative Research

Cooperative research projects are those projects, normally supported through grants, contracts, cooperative agreements or similar arrangements, which involve institutions in addition to the principal grantee or prime contractor (such as a contractor with the grantee, or a subcontractor with the prime contractor). In such instances, the principal grantee or prime contractor remains responsible to CDC for safeguarding the rights and welfare of human participants. However, each cooperating institution shall comply with the Federal Regulations except that in complying with the Federal Regulations institutions may use joint review, reliance upon the review of another qualified IRB (deferrals), or similar arrangements aimed at avoidance of duplication of effort, with approval of OPRR. The Human Subjects Office (for non-funded research) and the Procurement and Grants Office (for funded research) will be responsible for certifying that collaborative institutions have OPRR-approved assurances of compliance with the Federal Regulations and that collaborative institutions' IRBs have reviewed and approved the research.

CDC and Local IRB Reviews of Cooperative Research

For cooperative research conducted between CDC and a local site, a protocol and consent form should be developed that will be reviewed by the CDC IRB and the local IRB. It is recommended that the CDC IRB review the protocol and consent form prior to the review at the local level. Once approved by the CDC IRB, the local IRB should review and approve the protocol. If the local IRB changes the protocol and any supplementary documents, those changes must be reported and approved by the CDC IRB. For cooperative research involving CDC and multiple local sites, it is recommended that a protocol and consent form be developed and approved initially by the CDC IRB.

CDC Reliance Upon Another IRB of a Collaborating Institution

When CDC is one of the collaborative institutions in a collaborative research project, CDC's IRB will review and approve the research protocol. On rare occasions, CDC may choose to rely upon the review of another IRB, (i.e., defer to another IRB).

Criteria for Deferral

A CDC IRB review of a research project conducted in part by CDC investigators may be deferred to an OPRR-approved, non-CDC IRB when all of the following conditions are met:

1) The principal investigator is not an employee, contractor, visiting scientist or fellow of the CDC. This policy does not apply to a CDC employee who is assigned to another agency and who functions as an employee of that agency and lists his/her affiliation with the other agency and not with CDC.

2) CDC does not fund the research study. That is, for example, no grants, cooperative

agreements or contracts are issued by CDC in support of the research. In-kind salary support of the CDC investigator is allowed under this criterion.

3) CDC investigators do not have any direct interaction with study participants or possess individually identifiable data from the study.

4) The study has been granted approval by a non-CDC IRB of an organization that has a multiple project assurance from OPRR and is responsible for participant recruitment.

5) The study involves no more than minimal risk and does not address a controversial topic. 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. Controversial means sensitive such as illegal behaviors, sexual behavior practices, or psychiatric illness; involves a vulnerable population as defined in the Federal Regulations; or is of particular interest to the DHHS or Congress.

CIO Responsibilities

The CIO submits a written request for deferral to the Deputy Associate Director for Science. The request should address each of the criteria listed above in the following manner:

1) the identity of the principal investigator and his/her affiliation and the names of the CDC collaborators and their roles in the research study.

2) a statement that CDC has not contributed funds to the study.

3) a statement that CDC will not have direct interaction with study participants nor possess personal identifiable data.

4) evidence that an OPRR-approved, non-CDC IRB has approved the study; provide the name, address, phone number of the IRB's chair and of the IRB's administrator.

5) a statement that the study involves no more than minimal risk and involves no controversial issues.

A copy of the approved study protocol and consent forms must be attached to the written request. If the research study is approved for deferral, the Human Subjects Contact will submit a copy of any amendments or changes submitted to the non-CDC IRB as well as copies of all annual reports on the protocol and certifications of annual IRB review and approval.

Human Subjects Office Responsibilities

The CDC Deputy Associate Director for Science will determine whether deferral of CDC IRB

review is appropriate. If a decision is made to defer, the Deputy Associate Director for Science, will contact the non-CDC IRB to complete the Cooperative Amendment and submit it to OPRR.

When the Cooperative Amendment is approved by OPRR, the Deputy Associate Director for Science will notify the Human Subjects Contact who, in turn, will notify the CDC investigator.

CDC's decision to defer protocol review will be reviewed on an annual basis by the Deputy Associate Director for Science; an annual report and certification of annual IRB approval by the non-CDC IRB will be reviewed by the Deputy Associate Director for Science. The study protocol will be assigned a CDC protocol number and tracked as an active study protocol.

Certification of Assurance from Collaborating Institutions for Non-Federally Funded Research

CDC will enter into collaborative research studies only when the collaborating institution(s) have provided certification of an assurance of compliance with the Federal Regulations and of local IRB review and approval. Certifications of assurance and IRB review for nonfunded collaborative research will be handled by the Human Subjects Office.

When a research protocol is submitted to the CDC IRB for review, the CDC investigator will notify the Human Subjects Office (Atlanta), the IRB Administrator (NCHS), or the IRB Chair (NIOSH) of all collaborating institutions on the research study. The Human Subjects Office will determine whether the collaborating institution has an OPRR-approved assurance. For a domestic institution that does not have an assurance, the Human Subjects Office will notify the CDC investigator that the collaborating institution will need to obtain a single project assurance. The Human Subjects Office will prepare the single project assurance for the collaborating institution. Upon obtaining all necessary signatures, the assurance will be forwarded to OPRR for approval. For a foreign institution that does not have an assurance, the Human Subjects Office will prepare an international single project assurance or an international collaborative project assurance. CDC has set up an OPRR-approved cooperative protocol research program.

The CDC International Cooperative Protocol Research Program (ICPRP) will be used when an existing collaboration has been proven to be productive for CDC and the host country institution(s), and joint research projects are anticipated for the near and distance future. Research is considered to be involved (in accordance with 45 CFR 46) whenever CDC investigators are involved with sites covered by OPRR-approved Cooperative Project Assurances (CPAs) unless those activities are confirmed to be nonresearch by the Deputy Associate Director for Science. The ICPRP consists of multiple protocol collaborations involving or potentially involving multiple sites in one or more host countries. The ICPRP collaboration must be approved by the Deputy Associate Director for Science. The CDC International Cooperative Project Assurance will be reserved for multi-site, multi-protocol international collaborations involving the research areas listed above, and will be invoked only after CDC has an established history of productive collaboration with the host country. Single protocol collaborations will be covered through the international single project assurance mechanism. Each research protocol must be reviewed by a CDC IRB and by an OPRR-approved designated ethics committee (EC)

within each host country institution; for example the ministry of health.

ICPRP collaborations include:

Epidemiology protocols in infectious diseases.
Epidemiology protocols in HIV, sexually transmitted diseases, and tuberculosis.
Epidemiology protocols in environmental health and occupational health.
Vaccine-related protocols.
Therapeutic intervention protocols in infectious diseases.
Therapeutic intervention protocols in HIV, sexually transmitted diseases, and tuberculosis.
Therapeutic intervention protocols in environmental health.
Community intervention protocols in infectious diseases.
Community intervention protocols in HIV, sexually transmitted diseases, and tuberculosis.
Community intervention protocols in environmental health and occupational health.

Procedures for Providing, along with Host Country Collaborators, a CDC International Cooperative Protocol Research Program (CPRP) Assurance to OPRR:

1. A CDC staff person explains to his/her colleagues in the other country the option to obtain an approved CPRP Assurance in place of repeated single project assurances.

2. Both institutions agree that they would now prefer the efficiencies of a CPRP Assurance.

3. A CDC staff person provides a packet of CPRP material to the host country; the packet includes the latest OPRR-provided WordPerfect version of the CPRP form as well as several examples of approved CPRPs from other countries.

4. The CDC staff person explains CDC and OPRR requirements to host country collaborators and ethics committee chairperson, explains CPRP material and discusses options for host country ethical review.

5. The host country institution convenes appropriate ethics committee, if one does not already exist.

6. As part of their deliberation about accepting CPRP Assurance responsibility, host country committee reviews text instructions for completing CPRP.

7. A CDC staff person assists host country collaborators in preparing CPRP forms for submission to and approval by OPRR, including printing on institutional letterhead if available. If letterhead is not available, an official seal will be used.

8. The CPRP material, with original signatures, is carried by or sent by express mail to CDC contact person. (In emergency situations, a signed facsimile may be acceptable while the original is in transit.)

9. After obtaining other necessary signatures in relevant Division and CIO, the Principal Investigator or CIO contact person forwards CPRP material to the Deputy Associate Director for Science.

10. The Deputy Associate Director for Science signs on behalf of CDC.

11. CPRP packet is sent by Deputy Associate Director for Science to designated OPRR staff person.

12. OPRR reviews CPRP Assurance material.

13. OPRR staff address any concerns to the Deputy Associate Director for Science, who works with relevant CDC program and host country investigators and ethics committee to satisfy OPRR concerns.

14. Once OPRR concerns are satisfied, the principal investigator is notified and approval process for individual protocols proceeds in parallel in Atlanta (CDC IRB) and in host country ethics committee.

15. For renewal of this process, the same procedures are followed every five years.

Procedures for Obtaining a CDC International Single Project Assurance

1. A CDC staff person explains to his/her colleagues in the other country the need for CDC IRB review and the need for in-country review. The need for a single project assurance is discussed and agreed upon.

2. A CDC staff person provides a packet of single project assurance material to host country; the packet includes latest OPRR-approved Wordperfect version of single project assurance form as well as several examples of approved single project assurance from other countries.

3. The CDC staff person explains CDC and OPRR requirements to host country collaborators and ethics committee chairperson, explains single project assurance materials and discusses options for host country ethical review.

4. The host country institution convenes the appropriate ethics committee or decides to rely on another ethics committee.

5. As part of their deliberation about accepting the single project assurance responsibility, host country committee reviews text instructions for completing the single project assurance.

6. A CDC staff person assists host country collaborators in preparing single project assurance forms for submission to and approval by OPRR, including printing on institutional

letterhead if available. If letterhead is not available, an official seal will be used.

7. The single project assurance materials, with original signatures, is carried by or sent by express mail to CDC contact person. (In emergency situations, a signed facsimile may be acceptable while the original is in transit).

8. After obtaining the necessary signature in relevant division and CIO, the principal investigator or CIO contact person forwards the single project assurance materials to the Deputy Associate Director for Science.

9. The Deputy Associate Director for Science signs on behalf of CDC.

10. The single project assurance material is sent by the Deputy Associate Director for Science to designated OPRR staff person.

11. OPRR reviews the single project assurance materials.

12. OPRR staff will address any concerns to the Deputy Associate Director for Science, who works with relevant CDC program, host country investigators and ethics committee representatives to satisfy OPRR concerns.

13. Once OPRR concerns are satisfied, the principal investigator is notified and the approval process for protocol occurs.

The International Cooperative Project Assurance and Single Project Assurance can also be used for Federally-funded research. When PGO plans to fund a foreign institution, PGO will notify the Human Subjects Office. The procedures outlined above will apply.

<u>Certification of Assurance and IRB Review for Federally Funded Research</u>

Federal funds administered by CDC may not be expended for research involving human participants unless the requirements of 45 CFR 46 including all Subparts have been satisfied.

All research protocols involving use of federal funds must be reviewed by the Procurement and Grants Office (PGO) and meet the following requirements:

a. Assurances and Certifications

(1) During the initial administrative review of the applications or proposals by the PGO the application checklist must be reviewed for the use of human participants. A certification (Optional Form 310 or designation on the application form 398) must be provided with the application if humans are involved (whether or not the research is exempt). If certification is not provided, PGO must request it from the applicant.

Prior to review of the application by the Objective Review Group (ORG) or review of proposals, the CIO Human Subjects Contact official responsible for the review must determine that all human participants information has been included in the application or proposal so that the review committee can adequately evaluate protection for the participants. When an exemption from the regulations is designated in the application or on the Optional Form 310, the CIO Human Subjects Contact must ascertain that the designation is appropriate. The CIO Human Subjects Contact must also advise the review committee members of their responsibility to evaluate the protection of the participants.

(2) Applications or proposals lacking Definite Plans for the Involvement of Human Participants:

Certain types of applications for grants, cooperative agreements or contracts are submitted to CDC with the knowledge that human participants may be involved within the period of funding but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants where selection of specific projects is the institution's responsibility; research training grants where the activities involving participants remain to be selected; and projects in which human participants' 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 can be made. However, except for research exempted or waived under the Federal Regulations, no human participants may be involved in any project supported by the award until the project has been reviewed and approved by an IRB.

b. Review by the Objective Review Group

The Objective Review Group or review committee is expected to review the human participants protocol in the application. The review will take into consideration the risks to the participants, the adequacy of protection against these risks, the potential benefits of the proposed research to the participants, and the importance of the knowledge to be gained.

c. Recommendations of the Objective Review Group or Review Committee

For applications or proposals involving human participants, the review group may recommend:

(1) Approval of the application or proposal without any human participants restrictions;

(2) Approval of the application or proposal but with comments made to the applicant regarding human participants protections;

(3) Limitations of the work proposed, the imposition of restrictions, the elimination of

concerns relating to the protection of human participants prior to the release of an award; or

(4) Disapproval of the application or proposal if the research risks are sufficiently serious and protection against the risks is so inadequate as to make the entire application unacceptable.

d. Preparation of Summary Statements

A section must be provided in the Summary Statement reflecting the evaluation of the use of the human participants. If there are any restrictions, limitations, concerns and comments relating to the human participants, they must be addressed in the Summary Statement.

e. Pre-Award Review by CIO Officials

The CIO Human Subjects Contact must review each application to determine, prior to award of a grant, that all human participants concerns and protections which appear inadequate as noted by the Objective Review Group or review committee are satisfactorily resolved. Information regarding all restrictions and concerns about the human participants should be transmitted in writing by the Grants Management Office or Contract Office to the official signing for the institution, with a copy to the principal investigator.

f. Review and Award by the PGO

(1) Pre-award Review of Applications and Proposals

All applications and proposals having unresolved human participants concerns must have documentation from the CIO of the satisfactory resolution of the human participants concerns.

For each application or proposal, recommended for approval which is likely to be funded and which requires negotiation of an Assurance of Compliance (when the institution is not listed on the Multiple Project Assurance List), PGO will forward to the OPRR Assurance Coordinator as soon as possible a request for negotiation of an Assurance of Compliance. Attached to the request should be a copy of the application, summary statement, addenda, and information identifying the individual(s) at CDC who should be notified when the negotiation is completed and the assurance approved. OPRR will notify CDC of the approval of a satisfactory assurance.

During the month of September when there is insufficient time to obtain the single project assurance before the award must be made to meet CDC's award deadlines, OPRR has agreed to allow the award of grants with restrictions (language for the restriction provided

by OPRR) on the use of funds for research involving humans.

Where the research will be conducted by cooperating institutions, all of the cooperating institutions must have filed Assurances of Compliance with OPRR.

Before a year has elapsed between the IRB review date certified on the Optional Form 310 and the anticipated award date, PGO must require IRB re-review and certification by a validly dated Optional Form 310 prior to award.

PGO, Grants Management Branch places a code (30) in the Grants Management Information System (GMIS) Award Module for each award that involves human participants. This code serves as a reminder that the project involves humans as participants and that annual IRB reviews are required.

g. Review and Award of Noncompeting Continuation Application

PGO will ascertain the presence and completeness of the Optional Form 310 or designation on the application form 2590. Certification must be within 12 months preceding the requested award date. No award may be made until a proper certification is received by the PGO.

CIO Responsibilities

a. Identifies to PGO in the Program Announcement or the Request for Contract whether projects funded could involve humans as participants and should identify when CDC investigators will be involved in conducting the research.

b. Reviews application for human participants designation, appropriateness of exemptions, adequacy of information provided.

c. Reviews and clears research protocols before sending to Human Subjects Office when a CDC investigator is involved in the research study.

d. Follows up with applicant whenever designation is inappropriate or human participants-related information is lacking.

e. When appropriate, briefs IRBs and PGO regarding review of the human participants protocol.

f. Resolves concerns with Principal Investigators.

g. Resolves concerns with applicants to be funded.

h. Notifies PGO of any special restrictions in research procedures.

i. Monitors for changes in human participants involvement and projects without definite plans for human participants involvement (e.g., training grants).

PGO Responsibilities

a. Reviews documentation on any Federally funded research proposal where the research involves human participants. Coordinates with Human Subjects Office in determination whether proposal is research involving human participants and whether CDC investigators will be involved in the research.

b. Follows up with CIO officials if discrepancies exist.

c. Documents that assurances are in place and requests single project assurances where required and certifies IRB review and approvals.

Tracking CDC IRB Reviews of Federally Funded Research by CDC

In some cases CDC scientists will function as investigators for some grants, cooperative agreements, or contracts. It is necessary for PGO to be aware of and track research involving CDC investigators for two reasons:

1. The Program Announcement should state under the CDC Activities listed under the Program Requirements that CDC will work with the recipient to develop a protocol that will be reviewed and approved by all cooperating institutions' IRBs, including the CDC IRB.

2. Under Federal Regulations, 45 CFR 46, each cooperating institution in a research project is responsible for reviewing the research by an IRB. For those grants, cooperative agreements or contracts in which there are CDC investigators, CDC is defined as one of the cooperating institutions and must review the research project just as the awardee and other local sites must do. PGO needs to track initial and annual CDC, awardees and local site IRB reviews.

The following procedures will be implemented.

CIO Responsibilities

At the time of developing the Program Announcement:

1. If the project is research, CIO will insert a section on Human Subjects into the Program Announcement. It should read:

"If the proposed project involves research on human subjects, the applicant must comply with the Department of Health and Human Services Regulations (45 CFR 46) regarding the protection of human research subjects. Assurance must be provided to demonstrate that the

project will be subject to initial and continuing reviews by an appropriate Institutional Review Board. The applicant will be responsible for providing evidence of this assurance in accordance with the appropriate guidelines and forms provided in the application kit."

2. If the research project will have CDC scientists as co-investigators, the CIO will insert a section under the CDC Activities listed under the Program Requirements in the Program Announcement related to obtaining CDC IRB approval. It should read:

"Assist in the development of a research protocol for IRB review by all cooperating institutions participating in the research project.

The CDC IRB will review and approve the protocol initially and on at least an annual basis until the research project is completed."

At the time of funding program announcement applications:

CIO Responsibilities

1. When a CIO submits funding memoranda for new grants or cooperative agreements and for continuation of non-competing cooperative agreements, it will attach to the memoranda a research tracking form which describes whether the cooperative agreement involves a research project; if so, whether there are CDC investigators; and if so, whether the CDC IRB has reviewed and approved the protocol.

PGO Responsibilities

1. PGO will send a copy of the research tracking form to the Deputy Associate Director for Science.

2. PGO will track certification of CDC IRB review along with certification of IRB reviews from awardee. Funds will be released for use when all IRB certifications have been received.

Noncompliance by an Investigator

Common lapses in investigator compliance include unreported changes in protocols, misuse or nonuse of the informed consent document, and failure to submit protocols to the IRB in a timely fashion. Problems such as these are often caused by communication difficulties. With investigator goodwill, these cases can be resolved by the IRB without jeopardizing the welfare of research participants. Occasionally, an investigator will either avoid or ignore an IRB review. Such cases present a more serious challenge to the IRB and to the institution. Regardless of investigator intent, unapproved research involving human participants places those participants at an unacceptable risk. When unapproved research is discovered, the IRB and CDC will act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the investigator's

fitness to conduct human subject research. In addition, any serious or continuing noncompliance with the Federal Regulations will be reported to OPRR.

Noncompliance by an IRB

IRB noncompliance occurs whenever the IRB deviates from the duties imposed upon it by the Federal Regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective participants to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable participants; and failing to conduct continuing review of research at intervals appropriate to the degree of risk. IRBs also breach their regulatory responsibilities by failing to maintain adequate records of IRB business and to hold their meetings with a majority of members present, including a nonscientific member. A demonstrated inability to carry out IRB responsibilities in accordance with the Federal Regulations can be cause for the suspension or withdrawal of CDC's multiple project assurance.

REFERENCES

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