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Subject: Initial Review Considerations
Division: IRB
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IRB Policy 107.1: INITIAL REVIEW CONSIDERATIONS

Policy

All research proposals that intend to enroll human subjects must meet certain criteria before study related procedures can be initiated. The criteria are based on the principles of justice, beneficence and autonomy as discussed in the Belmont Report and are specified below. This policy applies to all initial reviews, whether they are conducted via expedited review or at a convened meeting.

Minimal Criteria for Approval of Research

1. In order for a research project to be approved, the IRB must find that:

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

    b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

2. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that 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 or benefits that fall within the purview of its responsibility.

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

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by appropriate local, state and federal regulations.

5. Informed consent will be appropriately documented as required by local, state and federal regulations.

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

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

8. When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence or for subjects found at international sites, additional safeguards have been included in the study and in the IRB review process, to protect the rights and welfare of these subjects.

Study Population

The prospective study population must be appropriate with respect to the nature and goals of the research. The IRB will examine carefully the characteristics of the subject population. Factors such as the required number of subjects, age range, sex, ethnic background and health status will be considered. The utilization of any vulnerable classes of subjects, such as fetuses, prisoners, children, and mentally incompetent persons, must be clearly justified. Although the use of vulnerable persons as subjects is not prohibited by any regulations or ethical codes, justification for their involvement in research generally becomes more difficult as the degree of risk and vulnerability increases.

Naturally, there are exceptions to the principle of "equitable selection of subjects." For instance, research involving the study of a disease which is prevalent in only one ethnic or racial group (e.g., sickle cell anemia and Tay-Sachs Disease) would not require the application of this principle.

In past years, the standard has been to exclude populations from participation in research activities when there is no evidence of safety in those populations. For example, pregnant women have been largely excluded from research because there is seldom safety data available for pregnant women and fetuses.

Every blanket exclusion of particular populations from potentially beneficial studies should be justified based on data from the literature on the drug/device/procedure being studied. It is important to note that the absence of data confirming safety is not equivalent to the presence of data confirming risk.

Treating Clinician as PI, Co-PI, Study Doctor

When the PI, Co-PI, or study doctor for a study may also be the participant's treating clinician, there is a potential for a conflict of interest. In the original IRB submission, the PI should describe how s/he will protect against undue influence or coercion.

To the extent possible, someone who is not directly involved in the treatment of a prospective participant should participate in the consent process.

This potential conflict of interest should also be disclosed to potential participants in the consent form. The following is an example of standard language that has been used in prior FRI approved consent forms:

> <u>Disclosure:</u>
> Your health care provider may be an investigator of this research protocol and, as an investigator, is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this research project. You are not under any obligation to participate in any research project offered by your doctor.

The IRB may require additional information or protections to address this potential conflict of interest.

Subject Recruitment

The IRB will review the method of prospective subject identification and recruitment in order to be assured that it is ethically and legally acceptable. Advertisements used to recruit subjects are considered an extension of the recruitment and informed consent processes and, therefore, must be reviewed and approved by the IRB.

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Experimental Design

While the IRB is not charged by Federal regulation with the responsibility of reviewing protocols for scientific merit, issues related to the adequacy of the scientific design often emerge during the review. Such issues as inclusion of adequate and appropriate controls, adequacy of sample size, and appropriateness of experimental endpoints may be raised in the review. The IRB will make a judgment on the validity of the study design as part of its assessment of the risk/benefit ratio, because no risk to subjects can be justified ethically if the study design is flawed to the degree that no useful information is likely to be forthcoming.

In reviewing any protocol, the IRB should be provided with complete information regarding experimental design and the scientific rationale (including the results of previous animal and human studies) underlying the proposed research, and the statistical basis for the structure of the investigation.

Deception of Research Subjects

It should be noted that while the IRB accepts the need for certain types of research to employ strategies that include either deception and/or withholding of information, use of such strategies must be fully justified. In general, deception is not acceptable if in the judgment of the IRB the subject would have declined to participate had they been informed of the true purpose of the research. For example, investigational drug studies, which require a "washout period" must generally be so informed.

When evaluating the use of deception in research, the IRB will discuss the following issues:

1. Validity of the research

2. Alternative methodologies
3. The characteristics, values, and morals of the experimental sample
4. Potential harm
5. Privacy and confidentiality
6. Informed consent.
    a) Although subjects may not be fully informed, they should be informed of as much as possible without threatening the ability of the researcher to test the true hypothesis of the study.
    b) FRI's recommendation is that the consent form should never be used as part of the deception and thus should not include anything that is untrue, and reveal as much as possible to the participant regarding the procedures in the study.
    c) The consent form does not need to detail specific elements of the study if this will eliminate the capability of the study to inform the process under investigation.

Potential Risks

Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the policies of FRI and existing federal regulations. One of the major responsibilities of the IRB, therefore, is to assess the risks and benefits of proposed research.

Risk is a potential harm (injury) associated with the research that a reasonable person, in what the investigator knows or should know to be the subject's position, would be likely to consider significant in deciding whether or not to participate in the research. The concept of risk includes discomfort, burden, or inconvenience a subject may experience as a result of the research procedures. Underlying the consideration of risk is the implicit moral guideline that all investigators have a duty to not harm their subjects and must minimize potential risk to the greatest extent possible.

In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies subjects would undergo even if not participating in research, will be considered. For example, if the research is designed to measure the behavioral results of physical interventions performed for therapeutic reasons (e.g., effects on memory of brain surgery performed for the relief of epilepsy), then only the risks presented by the memory tests will be considered when the IRB performs its risk/benefit analysis. It is possible for the risks of the research to be minimal even when the therapeutic procedure presents more than minimal risk. FRI's IRB will recognize, however, that distinguishing therapeutic from research activities can sometimes require very fine line drawing. Before eliminating an activity from consideration in its risk/benefit analysis, the IRB will be certain that the activity truly constitutes therapy and not research.

Minimal Risk vs. Greater Than Minimal Risk

Minimal risk is broadly defined as the probability of and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life [of the proposed study subjects -- may be broadened if approved by the IRB] or during the performance of routine physical or psychological examinations or tests (e.g., collection of urine, collection of sweat, weighing, pulse measurement, voice recordings, electrocardiography).

The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. Minimal risk for prisoners "is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons."

Once the risks have been identified, the IRB will assess whether the research presents greater than minimal risk. The IRB may use the expedited review process for proposals, which meet certain conditions.

The approval letter that is sent to the investigator following the IRB approval of the study will note the risk classification and how often it will be reviewed by the IRB.

In research presenting more than minimal risk, potential subjects must be informed of the availability of medical treatment and compensation in the case of research-related injury, including who will pay for the treatment and the availability of other financial compensation.

Determination that Risks are Minimized

Risks, even when unavoidable, can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration. The IRB is responsible for assuring that risks are minimized to the extent possible.

The IRB will analyze the beneficial and harmful effects anticipated in the research, as well as the effects of any treatments that might be administered in ordinary practice, and those associated with receiving no treatment at all. In addition, it will consider whether potentially harmful effects can be adequately detected, prevented, or treated. The risks and complications of any underlying disease that may be present must also be assessed.

Potential Benefits

A benefit is a valued or desired outcome. Benefits associated with participation in research can be classified generally as those that accrue to the subject directly (e.g., improvement of the subject's health status, acquisition by the subject of knowledge considered of value) and those that accrue to society (e.g., additions to the knowledge base). The IRB will review the anticipated benefits to both the subject and to others. In addition, the IRB will consider whether the benefits are maximized to the greatest extent possible through proper protocol design. Therefore, an underlying moral notion of beneficence should guide the investigator.

Financial or other forms of compensation are not considered a benefit to be derived from research participation. Although the subject may consider financial compensation a desirable outcome, this fact will not be used in the risk-benefit analysis.

Risk-Benefit Analysis

Once the potential risks and benefits are identified, the IRB will examine the relationship of the risks to the benefits. Risks and benefits cannot be considered parallel constructs and, therefore, no formula is applicable. The various ethical codes and regulations, however, require a favorable balance between harm and benefit.

In research that has no likelihood or intent of producing a diagnostic, preventive or therapeutic benefit to the subject (non-therapeutic research), the potential risk to the subject must be outweighed or balanced by the potential benefit to the subject and/or by the potential benefit to society.

In research involving the study of the efficacy of a therapeutic or diagnostic method and the intervention is, therefore, not designed solely to enhance the well-being of the subject who is seeking a health benefit (therapeutic research), the potential risk should be primarily outweighed or balanced by the potential benefit to the subject. In addition, the relationship of the potential benefit to the risk must be at least as favorable to the subject as that presented by alternate standard therapies available to the subject in the

non-research context. No subject is allowed to continue participating in a research protocol if therapy of proven superior nature becomes available to the subject.

In research where a standard therapy not part of the research protocol is employed solely for the benefit of the subject along with additional procedures performed solely for research purposes, the potential benefits of the therapy will not be used to justify exposing subjects to the risks associated with the research procedures. Such risks can only be justified in light of the potential benefits of the research procedures. Conversely, only the risks associated with the research procedures will be used in determining the risk-benefit ratio.

Subject Compensation

The IRB will review the amount of compensation (monetary as well as other forms), and schedule of all payments in order to be assured that neither are coercive or present undue influence. Actual/estimated costs, such as for transportation and child care, may be the basis for payments to the study subjects.

Tax Information:
All payments to participants constitute income to the individual study participant and should be included in that individual's income tax return. For payments for study participation in excess of $600, in cash or any items of value (including vouchers, gift certificates, goods, etc.), in a calendar year, FRI is required to issue a 1099. Therefore, if subjects will be paid more than $600 for their participation, the following paragraph should be included in the Reimbursement/Compensation section of the informed consent document:

> "If you complete this research study you will receive at least $600 for your participation. As a result, you must complete IRS Form W-9 before the research begins. This form contains your name, address, and social security number and will be submitted to Friends Research Institute's Accounting Office. At the end of each year FRI will issue an IRS Form 1099-Misc to you, and the Internal Revenue Service. This Form tells you and the Internal Revenue Service that a payment was made to you for your services, but it does not say that you were paid for participation in a research study. That information will remain confidential. You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive."

A participant may refuse to give his/her social security number or a participant may not have one. The IRB recommends that if a potential participant does not have, or refuses to provide a social security number, then s/he may choose not to participate in the study.

The IRS provision is for payment of $600 per year, not per study.

Confidentiality

The IRB will review the methods to be used to reserve confidentiality. If research data with subject identifiers will be made available to persons other than the listed investigators, sponsor or federal agency, the IRB will review the justification for sharing this data and determine acceptability.

Certificates of Confidentiality should be obtained for studies collecting information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

Researchers with a Certificate of Confidentiality are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self

or others. Therefore, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

Informed Consent

IRB Policy 108.1

Audiotaping, Videotaping, and Still Photography

Investigators' plans for recording data should receive prospective IRB review and be included in the informed consent process. Plans to destroy, share, or archive the recordings should also be discussed with the IRB and with study participants. If an investigator chooses to archive recordings but obscure the identities of participants in publication, then plans for protecting the confidentiality of the original study records must also be addressed.

Occasionally, although investigators prefer to record or photograph participants, they state that they could carry out their research without such recordings. In these cases, participants should be provided with an opportunity to consent or decline to consent to recordings. This may be assured by providing separate consent forms, one to participate in the research, and one to participate in the recordings.

Review of Investigator Qualifications

The IRB will review investigator qualifications and must be assured that:

1. The investigator has the appropriate qualifications and licensure to carry out the procedures involving human subjects with an acceptable degree of risk, and

2. The investigator has adequate facilities to conduct the research with an acceptable degree of risk.

State Laws and Regulations

Every state has its own statutes, regulations, and case law that may impose requirements on the research process that add to or are different from what federal law requires. Although some federal laws in essence "overrule" conflicting state laws, this is generally not the case with state laws relating to the research process. These laws vary considerably from state to state.

The IRB will review the following, to make sure that the protocol is consistent with state regulations:

1. Age of consent
2. Capacity to consent/legally authorized representative
3. Children's assent
4. Informed consent
5. Genetic research
6. Confidentiality of medical records
7. HIV/STD reporting requirements
8. Mandatory reporting requirements
9. Laws about referral fees and recruitment methods
10. Laws governing clinical research, and investigational drugs
11. Laws about vulnerable patients
12. Laws about medical practice and delegation of authority to perform procedures.

Determinations

After the IRB has discussed the protocol, consent form, and supporting documents, the IRB will determine if the requirements of 45 CFR 46.111 (21 CFR 56.111) have been satisfied. If the requirements have not been satisfied, the IRB will not approve the study. If the requirements have been satisfied, the IRB will discuss whether the study should be approved or not.

Once the IRB has voted to approve a study, the IRB will make a risk determination for the study, and then determine the review period. Studies are reviewed at periods appropriate to the degree of risk subjects are exposed to due to their participation in the study, but at least annually. The IRB determines a review interval for the research as appropriate to the degree of risk, but not greater than one year from the last date of IRB approval. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of the research occurs on or before the date when IRB approval expires.

The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

1. Involvement of vulnerable populations;
2. Research conducted internationally;
3. Use of waiver of informed consent procedures, (e.g. surrogate consent);
4. Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events;
5. Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns; and/or
6. Recommendations from institution.

On occasion, the IRB may also determine that the PI should submit a periodic report prior to the date of the continuing review. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. These types of reports will be requested when the IRB feels that it is necessary to be updated on specific information within a certain time frame, however, it does not deem it necessary to conduct a complete continuing review at this time. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report.

If Subparts B, C, or D are applicable to the research, the IRB will review the research under the appropriate subpart and determine if the requirements have been satisfied.

Responsibility

IRB Administrators are responsible for ensuring that IRB reviewers have the tools they need to complete their research reviews. IRB Reviewers are responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

Applicable Regulations and Guidelines

45 CFR 46.111
21 CFR 56.111