Understanding Institutional Review Boards: Practical Guidance to the IRB Review Process
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What is This?
ABSTRACT: The purpose of this paper is to provide practical guidance to assist investigators in the preparation of materials and obtaining approval for research projects that require oversight by an institutional review board (IRB). The central requirements for IRB approval and core considerations of IRBs are described. Specific suggestions for investigators regarding how to prepare their IRB applications to anticipate and address potential IRB concerns and questions are proposed. When researchers are familiar with these criteria and how they may be interpreted by an IRB, they can avoid deferrals or lengthy requests for protocol modifications or clarifications. General tips regarding the preparation of IRB submission materials that may allow for a smoother IRB review process are also discussed. A brief list of additional resources for investigators is appended.

In 1966, a system of local oversight designed to protect human subjects was initiated in the United States after scandals involving troubling, if not necessarily unethical, research studies were published.¹ The National Institutes of Health (NIH) Policy for the Protection of Human Subjects established the institutional review board (IRB) as the fundamental component of a system to protect human research subjects. Today, all federally funded or regulated research must be approved by an IRB.² In practice, especially at academic institutions, such review and approval is often required irrespective of the funding source or use of U.S. Food and Drug Administration (FDA)–regulated drugs and devices. Whether conducting minimal-risk survey research or engaging in a complex multicenter drug trial, researchers must learn to navigate the IRB review process.³ [Federal regulations define minimal risk as any risk where “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.”]

Unfortunately, many researchers find this process to be frustrating and difficult to understand. Although many factors can contribute to making the review process more difficult than necessary, the complexities and nuances of the IRB review process can contribute to the level of frustration researchers may experience. Better understanding of the primary determinations an IRB is required to make during the review process can help researchers anticipate problematic issues and provide the information relevant to these determinations in their IRB applications. This paper will provide an overview of the central features of IRB review and required determinations, along with practical advice for preparing IRB applications and associated study materials. Although conventions and regulatory interpretations vary among institutions, this paper will describe the most common foundations of IRB review, and provide practical guidance that can minimize the difficulties researchers sometimes encounter during the IRB review and approval process.

Overview of IRB Review Criteria

Pursuant to the Common Rule (described below) and FDA regulations, specific criteria must be met for an IRB to determine that a protocol can be approved for the involvement of human subjects. When researchers are familiar with these criteria and how they may be interpreted by an IRB, they can craft an IRB application that anticipates many of the questions that arise during IRB deliberations, thus avoiding deferrals or lengthy requests for protocol modifications or clarifications. The primary criteria that IRBs follow are found in what is called the Common Rule, the set of federal regulations governing human subjects research, followed by several federal agencies and codified in 45 CFR 46.⁴ An overview will follow of the criteria used for IRB approval (as specifically codified in 45 CFR 46.111),
as well as an analysis of how IRBs apply them. [In accordance with federal regulations, studies may fall into 1 of 3 review categories: full, expedited, or exempt. The focus here is on the criteria IRBs use to conduct full and expedited reviews. The regulatory criteria for review of exempt studies are different and are implemented in a variety of ways among institutions. For guidance on how IRBs review studies that may qualify for exemption, researchers are encouraged to consult with their own IRBs. In addition, suggestions are included for researchers to help ensure their applications demonstrate to the IRB that the proposed research project meets the criteria for approval.]

**IRB Review Criteria 1: Ensuring That Risks to Subjects Are Adequately Minimized**

Federal regulations and IRBs recognize that research often presents risks to subjects. However, it is incumbent on investigators to ensure that the proposed research does not expose subjects to undue risk. Within an IRB application, investigators can specifically describe the scope of the risks of the research, and the steps taken to mitigate or eliminate risks to the degree possible. When reviewing applications to determine whether the risks of the research have been minimized, IRBs must also determine what risks are present. Although physical risks (eg, pain, discomfort, side effects) usually are described in IRB applications, often investigators do not acknowledge other risks, such as those that are social, psychological (suicidality), emotional (invasion of privacy, loss of confidentiality, harassment), economic (damage to reputation, loss of insurance, impact on employability), or legal.

The following represent questions that IRBs frequently ask about the risks of research and their expectations of how these risks have been minimized:

- **Do the protocol’s eligibility criteria adequately minimize risks to subjects?** IRBs review the protocol to determine whether the proposed subject population has been selected to ensure that risks to them are as low as possible. For example, if a drug being tested is primarily metabolized through the liver, the IRB would expect the protocol to ensure that only subjects with adequate hepatic function would be included in the study. Should a researcher wish to include patients who may be at some risk for liver damage and believe this group of subject population is critical to the study, the IRB application should provide a specific rationale for this. The IRB would need to understand why subjects at potentially higher risk should be included. IRBs also review eligibility criteria to ensure that the least vulnerable participants will be selected for the study. For example, unless a condition disproportionately affects children, an IRB would expect that a study of an experimental drug for which no or limited clinical data exist to be tested in adults first. The inclusion of the least vulnerable subjects is discussed further in the section on equitable subject selection.

- **Is subject monitoring sufficiently robust?** In addition to presenting eligibility criteria to select subjects who are exposed to the lowest possible risks, it is helpful to the IRB if researchers explicitly describe how the study procedures eliminate or mitigate risks and discomforts to subjects. IRBs pay particular attention to the proposed monitoring procedures outlined in a protocol. For example, if adverse changes in heart function are potential side effects of a drug being tested, the IRB would expect the protocol to include cardiac monitoring tests to be performed at an appropriate frequency, in addition to outlining eligibility criteria that eliminate participants with potential existing cardiac conditions that may put them at increased risk. In this example, the investigator should explain how the type and frequency of the proposed cardiac monitoring allows sufficiently prompt detection of changes in heart function such that this event can be reversed or halted before a significant impact on subjects’ health occurs. Researchers should also ensure that the protocol describes any required follow-up to detect potential delayed or long-term effects of study procedures.

- **Are the proposed study procedures well justified, reasonable, and as comfortable as possible for participants?** It is beneficial for researchers to describe in their IRB applications why procedures, especially those that may not be apparently connected to the research question, are essential to study goals. In addition, researchers should emphasize instances when procedures conducted specifically for the study will be combined with procedures that subjects are already scheduled to undergo for nonresearch reasons (eg, for usual clinical care). For example, if subjects have a bone marrow biopsy as part of their usual care, then investigators should make efforts to arrange that biopsy samples collected for research purposes are taken at the same time. If a study procedure is unusual, the IRB application should include an explicit justification for the procedures as well as some background regarding the rate of complications or adverse events.

- **How do the risks to subjects for research procedures compare with standard of care?** When preparing an IRB application for a clinical trial, it is helpful if researchers ensure that the document is specific in (a) what procedures are performed solely for research purposes vs those that are performed as part of clinical care and (b) how participation in the research study
differ from treatment the patient would undergo if they were not in the study. This information is critical for the IRB to determine the relative risks of the research vs risks experienced outside of the research study. The closer the risks of the research are to the standards of care, for example, the less likely IRBs will have concerns about the proposed study.

- **Are the research personnel qualified and appropriately trained to carry out the study procedures?** Most institutions now require all personnel engaged in human subjects research to undergo and document that they have completed training in ethical principles and regulations governing such research. IRBs must also ensure that the individuals conducting the research have the appropriate technical training to carry out study procedures. It is helpful for researchers to clearly identify the roles, credentials, and experience of the research personnel. For studies involving physical interventions, IRB applications should include details regarding the level of medical supervision believed to be adequate. For sociobehavioral studies, researchers should describe any training required for study personnel conducting interviews or engaging in observational research. When students or researchers in training interact with research participants, the IRB application should describe the training and oversight these individuals will receive before commencing research activities.

- **Are the procedures adequate for halting a specific study procedure or removing subjects from the study?** When procedures are conducted solely for research purposes, ensuring that a plan is in place which clearly outlines when procedures will be stopped is critical. Having specific rules for a protocol ensures that research personnel do not inadvertently increase risks to subjects because of an unintended ambiguity.

- **Is the research being performed in an appropriate location?** IRBs also assess if the research personnel are appropriately trained to carry out the study procedures. Most institutions now require all personnel engaged in human subjects research to undergo and document that they have completed training in ethical principles and regulations governing such research. IRBs must also ensure that the individuals conducting the research have the appropriate technical training to carry out study procedures. It is helpful for researchers to clearly identify the roles, credentials, and experience of the research personnel. For studies involving physical interventions, IRB applications should include details regarding the level of medical supervision believed to be adequate. For sociobehavioral studies, researchers should describe any training required for study personnel conducting interviews or engaging in observational research. When students or researchers in training interact with research participants, the IRB application should describe the training and oversight these individuals will receive before commencing research activities.

### IRB Review Criteria 2: Ensuring Risks to Subjects Are Reasonable in Relation to Anticipated Benefits

Many IRBs refer to this criterion as assessing the risk/benefit ratio of the research study and view this as the most important ethical determination they make. Some of the factors that are considered as part of assessing the risk/benefit ratio of a research study were outlined in the previous section. This section will discuss how an IRB may evaluate the acceptability of risks in relation to the potential benefits of the research. As the IRB Guidebook published by the Office for Human Research Protections describes, the risk/benefit assessment is not a technical one valid under all circumstances, because it is a judgment that often depends on prevailing community standards and subjective determinations of risk and benefit. Due to the nature of the process of the risk/benefit assessment, investigators may find that different IRBs can make different assessments of the risk/benefit ratio for the same study.9

In order to assess the risks in relation to the benefits, IRBs must first identify the risks of the protocol. Once identified, the IRB must determine the degree and likelihood of risks to subjects. Some questions that the IRB considers for identification of the level of risk the research presents to subjects include:

- **Are the risks participants will experience different from the risks of standard therapy or, if participants are not patients, everyday life?** Studies presenting risks to subjects that are similar to those of standard treatments and daily life tend to be less problematic for IRBs.

- **What are the frequency, severity, and reversibility of the risks to subjects and are there possible delayed effects of the study intervention?** If the risks of the research are easily reversible, are temporary, or represent a minor inconvenience, the IRB is likely to see the risks as acceptable as long as the study results in benefits to subjects, science, or society. Risks that are theoretical or potential have delayed effects tend to be more difficult for IRBs to assess.

- **Are there any characteristics of the proposed subject population that increase their risks?** Some populations may be more vulnerable than others due to their age, physical or emotional maturity, comorbidities, economic or social status, or education level. Two examples of populations that may be at higher risk are children and the elderly. Both may exhibit physiologic differences from adults (in the case of children) or younger adults (in the case of the elderly). If a drug has not been previously tested in these age groups, the IRB would need to know whether the expected risk profile is altered in any way due to potential physiologic differences.
● Are there potential differences in perception of risks among subjects? IRBs take into consideration the relative risks to the subject population. In patients with metastatic cancer, the risk of death from a treatment may be perceived as acceptable. However, risk of death generally would not be acceptable for people being treated for a condition that was not life threatening or severely debilitating.

● In the case of clinical research, what preclinical and clinical data are available to support the safety, efficacy, or dose level of the treatment? It is important for researchers to conduct literature reviews to ensure IRBs are presented with the most updated information about the side effects and efficacy of a drug or device, as well as whether the research question has yet to be answered definitively. In addition, the study design should be commensurate with the stage of the research. If little is known about the risks of a drug in humans, the IRB will expect the number of subjects exposed to the drug and its unknown risks to be as few as possible.

● In the case of sociobehavioral research, what types of data will be collected and are the methods to be used validated? Researchers should describe what types of data they will be collecting and include copies of any instruments that will be used, such as surveys, questionnaires, or interview scripts. It is beneficial to researchers to ensure that the instruments they propose to use are clearly consistent with the goals of the study. If any instruments contain sensitive questions, researchers should explain how these fit with the project’s goals, as well as how they are appropriate for the proposed subject population.

● Is the proposed drug dosing, drug administration route, or use of a device consistent with, if applicable, its approved labeling such that the proposed use in the patient population is unlikely to result in a significant change to the risk profile? If FDA-approved drugs are used in research but subjects may receive a higher dose of a drug than is standard, or the drug is administered in a new way, the potential risks of this alteration should be described specifically in the IRB application. Similarly, any different risks that may result from the novel use of a device should be addressed in the IRB application.

● In the case of clinical research, will any treatments be withheld from subjects, will the study involve a washout period, or will subjects be asked to abstain from their current medications? If the protocol involves any of these situations, the situation(s) should be directly addressed in the IRB application. In particular, the researcher should justify these procedures, acknowledge the risks of withdrawing or withholding medications, and describe how the concomitant risks will be mitigated. In some cases, more frequent study visits or follow-up telephone calls would be expected.

● How does the type of study design affect risk level? The most problematic study designs that IRBs encounter tend to be uncontrolled and open-label studies. Open-label studies involving investigational drugs often are added as extensions to phase III studies. Because there is no comparison group in the open-label study design, assessing the safety and efficacy of the study drug during the study is more difficult and may increase risks to subjects. In addition, the ability of the study to reveal the relationship of adverse events to the study drug is greatly diminished. If open-label studies are conducted before data from a double-blinded, controlled trial are analyzed, it may put subjects at risk for longer periods of time because it is not yet known whether the investigational agent is safer or more effective than its comparator.

When IRBs have determined the extent and nature of the risks a study presents, they then consider the potential benefits of the study. Benefits of a research study are generally thought of in terms of benefits to subjects and benefits to society. Occasionally, researchers will describe subject remuneration, free healthcare, or the opportunity to help others as benefits of the research. The federal agencies overseeing human subjects research, however, do not view these as factors, which are not part of the study’s design, that constitute benefits and thus they do not enter into the IRB's analysis of benefits and risks.

According to its assessment of the risks presented by the research and whether the research presents potential benefits directly to subjects or society, the IRB then must determine whether the risks to subjects are justified by the potential benefits and, thus, whether the research can be approved. The following is an outline of the potential outcomes of the IRB’s assessment of the risk:benefit ratio of a protocol:

● The study presents the potential for direct benefit to subjects. In this case, a higher level and degree of risks incurred by the subjects can be accepted by an IRB as ethical, especially when subjects may have no or limited therapeutic options available to them. However, in any study of an experimental treatment, the risk:benefit ratio should be as similar as possible to those presented by any available alternative therapy. IRBs must still ensure that the risks to participants are adequately minimized.

● The study does not present the potential for direct benefit to subjects but will benefit science or society. In this case, strong justification for the research question must be presented by the investigator, the risks to participants should be relatively low, and particular care must be
taken to minimize risks to subjects. A higher level of risk may be acceptable if the scientific question is of such importance to justify them. IRBs expect that this type of research generally will not be conducted in vulnerable populations. Additionally, it is especially important for this type of research to have a robust study design and sample size justification to minimize the number of subjects exposed to the risks presented by the research.

- The study does not present the potential for direct benefit to subjects and there is no clear or expected benefit to science or society. Generally, research in this category can only be approved if it presents no risks to subjects. Some IRBs refuse to approve such studies because they feel this research is unethical. Because student and trainee research frequently falls within this category, many IRBs will approve such research in recognition of the potential contribution to the professional or educational goals of the trainees, as long as any risk to subjects is remote and the subject population is not vulnerable. Research presenting any risk to subjects in the absence of any direct or societal benefit is ethically unacceptable and does not meet the federal requirements for IRB approval.

**IRB Review Criteria 3: Equitable Selection of Subjects**

Under this criterion, the IRB must ensure that selection of subjects is equitable. In making this assessment, the IRB takes into account the purposes of the research and the setting in which the research will be conducted. The IRB is particularly cognizant of special concerns that may be raised by research involving vulnerable populations, such as children, prisoners, pregnant women, people with disabilities, or others who are likely to be vulnerable to coercion or undue influence. When reviewing research involving these populations, the IRB must ensure that additional safeguards are provided to protect the rights and welfare of participants.

In considering whether the selection of subjects is equitable, the IRB will likely consider a number of questions, including the following:

- Is the target population appropriate to answer the research question? This is an especially important concern when particular ethnic or socioeconomic groups are targeted for study participation. The IRB will look for sufficient justification from the investigator for such targeting.
- Are any individuals being excluded from a study or being targeted for inclusion without sufficient justification? Although no population should be inappropriately targeted for inclusion, no population should be specifically excluded without reason. For example, adult clinical trials are not designed for enrollment of children, and pregnant women should not be enrolled in studies using known teratogenic agents.
- Will the proposed subject population benefit from the outcome of the research? Determining whether selection of subjects is equitable depends in part on whether the subject population will benefit from participation in the research, particularly if vulnerable populations are enrolled. For example, enrollment of individuals with impaired decision-making may be appropriate for studies investigating Alzheimer’s disease that may benefit that population. For sociobehavioral studies, results from research targeting particular ethnic or socioeconomic groups that can be shared with and used by these communities may constitute a benefit.

When preparing their IRB applications, researchers should explain why a particular subject population is appropriate for enrollment in their study. Researchers who plan to enroll populations for which specific federal regulations exist (eg, children, prisoners, pregnant women) should familiarize themselves with those requirements and be sure that their application adequately addresses them. The IRB staff is typically knowledgeable about these requirements, and researchers should contact their IRBs if they have questions about enrolling vulnerable populations and any additional application requirements. Researchers also should make certain that their application includes a robust consent process that is appropriate for the population(s) they wish to enroll. Although providing good informed consent or assent forms is an important part of this, researchers should ensure that the consent process addresses any special concerns raised by their subject population (eg, assessment of capacity to consent for subjects who may have impaired decision-making). Giving the IRB sufficient information about the subject population and the consent process will greatly assist the IRB in its assessment of the equitable selection of subjects and allow for a smoother review process.

**IRB Review Criteria 4–5: Informed Consent**

Informed consent is a key component of the Common Rule, requiring IRBs to determine that informed consent will be sought from each prospective subject or the subject’s legally authorized representative, and that informed consent will be appropriately documented. The Common Rule, as well as FDA regulations, assumes that, with a few exceptions, written informed consent will be obtained before any research procedures commence. IRBs must ensure that requests to waive informed consent or documentation of informed consent are justified and meet the appropriate regulatory requirements. When reviewing studies, IRBs assess the proposed consent process (not just the form),
including whether it is appropriate for the subject population. In assessing whether a proposed study meets the regulatory criteria regarding informed consent, the IRB will consider a number of questions, including the following:

- **Is an informed consent process described in the application?** Although appropriate consent forms are important, the process through which consent is obtained is also critical. A good consent process should at least provide adequate time for potential subjects to make an informed decision and ask the researchers any questions they may have regarding study participation.

- **Is the consent process appropriate for the subject population?** Special consent processes may be required for subjects with impaired decision-making or who are illiterate, blind, or have limited English language abilities. For example, when enrolling blind people or those with low literacy, a witness to the consent process and special documentation may be required. It is often recommended that the witness be an impartial third party. In addition, investigators should consider providing subjects with an audiotape of the consent process so that the subjects are able to reference it later. The additional protections that may be afforded by such special consent processes are also a way for investigators to help minimize risks when enrolling vulnerable populations and should be detailed in the IRB application.

- **Does the consent document(s) contain the required elements of informed consent?** The Common Rule requires consent documents to include 8 distinct elements, as detailed in Table 1. The federal regulations also outline additional elements of consent that the IRB may require in the consent documents. In addition to ensuring that the requisite elements are included, the IRB will assess whether the consent document is written at an appropriate reading level for the subject population. This can be particularly challenging when the study is a complex clinical trial or the subject population has limited literacy levels.

Researchers can assist in the IRB's assessment of informed consent by providing a detailed description of the consent process. Stating only that written informed consent will be obtained is generally not regarded as a sufficient consent process. The consent process should ensure that no human subjects are involved in the research before obtaining consent, unless informed consent has been waived by the IRB. The process should be designed to give potential subjects sufficient time and space to make their decision about research participation. A sound consent process should be conducted in a setting that allows a free choice to accept the invitation to participate or to refuse to participate without prejudice or penalty. Individuals who conduct the consent process should be well qualified and able to ensure that any questions potential subjects have are adequately addressed. If any vulnerable populations will be enrolled, the consent process should include additional safeguards as appropriate. (For example, the consent process for studies enrolling children should indicate how a child's assent and parental consent will be obtained.) A good description of a consent process will address these issues in detail, thereby making it easier for the IRB to determine that a sound process is in place.

When drafting consent documents, researchers can often rely on resources provided by their own institutions, which may include specific formatting requirements or consent form templates. Some general tips for writing consent documents include keeping the reading level low, usually between a sixth and eighth grade reading level. Using short sentences and subsections to break up information can also assist with making a consent document more accessible to potential subjects. Technical terms should be avoided and simpler words used instead. Using a font that is no smaller than 12 point
can help enhance readability (for aging populations, or studies of eye disease, larger font may be appropriate). Consent documents should avoid wording that is, or may seem to be, coercive or overly reassuring to a potential subject. Flowcharts and tables can help convey information about complicated study procedures or study visit schedules. Claims about the safety or efficacy for investigational articles or procedures should be avoided. Giving the consent form a version number and date can be helpful for study personnel, especially when changes need to be made to the form.

Some studies may qualify for a waiver of informed consent or waiver of documentation of informed consent. These are 2 different types of waivers that may be granted in different circumstances. Under the Common Rule, an IRB may approve a consent procedure that does not include or that alters some or all of the elements of informed consent, or may waive the requirements to obtain informed consent, provided that:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. the research could not practically be carried out without the waiver or alteration; and
4. the subjects will be provided with additional pertinent information after participation, where appropriate.

Research studies that involve prospective, direct interaction with subjects generally do not meet the criteria for a waiver of informed consent. IRBs generally do not accept inconvenience to the researcher as a justification for a waiver of informed consent. In no case should a researcher seek to withhold information about the research or the subject’s role solely to reduce the chances of refusal to participate. Requests and justification for a waiver of informed consent or a waiver of some elements of informed consent should be well described in the IRB application.

An IRB may waive the requirement for written informed consent (ie, documentation is waived, but the informed consent process is not) if it finds that:

1. The only record linking the participant and the research would be the informed consent document and the principal risk in a breach of confidentiality would be the potential harm; or
2. The research presents no more than minimal risk of harm to participants and involves no procedures for which written informed consent is normally required outside the research context.

This type of waiver of documentation applies especially to anonymous interviews (including face-to-face and telephone interviews) in which the investigator’s sole knowledge of the identity of the interviewee would come from the informed consent document. It is important to note that waivers of documentation of informed consent are not permitted in FDA-regulated research in most cases.

In the case when a potential waiver of informed consent documentation may apply, researchers should describe in the IRB application their plan for obtaining informed consent from subjects (eg, providing subjects with an information sheet, obtaining oral consent).

**IRB Review Criteria 6: Monitoring Data Collected to Ensure the Safety of Subjects**

Most IRBs require the presentation of a data and safety monitoring plan (DSMP) when the research presents more than minimal risk to subjects. A DSMP is a description of how the investigator or study sponsor will monitor research data and respond to adverse events and unanticipated problems that occur during the course of the research to ensure the safety of participants and the validity and integrity of data collection. Monitoring research is important because preliminary data may signal the need to change the research design, change the information presented to subjects or provide them with information that may affect their willingness to continue their participation, or even to terminate the project before the scheduled end date. Both the timing and adequacy of the plan for data analysis are important, especially to detect when the data suggest a need for early termination due to evidence of efficacy or futility, high mortality rates, accrual problems, or previously unrecognized safety problems. For long-term studies involving a significant number of subjects (eg, phase III clinical trials), IRBs tend to prefer that formal data and safety monitoring boards be established to review study data. If such a board will not be formed, it is especially critical to describe how adverse event trends will be identified, who will review unblinded or aggregate data, and that IRBs will be informed of adverse findings promptly.

Concerns about data and safety monitoring are not limited to biomedical research and, depending on the nature of the study, researchers conducting sociobehavioral research should also be prepared to provide a plan for monitoring subject safety. A sound safety monitoring plan is often essential for an IRB to approve higher-risk sociobehavioral studies, such as research on child abuse, drug use, or mental health issues. Survey or interview research that may reveal suicidality, potential for harm to self or others, or illegal behaviors should include provisions for handling such situations. This is particularly important because local or state law may require reporting of these events, and a certificate of confidentiality (COC; discussed below) may be needed to protect both the researcher and study participants.

**IRB Review Criteria 7: Protection of Subject Privacy and Data Confidentiality**

For research to be approved by an IRB, the protocol generally must include adequate provisions...
to protect the privacy interests of research participants and the confidentiality of research data. Privacy refers to a person's desire to control the access of others to him or herself. For example, research participants may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Confidentiality refers to the researcher's agreement with the participant about how the research participant's identifiable private information will be handled, managed, and disseminated.

An invasion of privacy or breach of confidentiality has the potential to present significant risk to subjects. Some information may, if a breach of confidentiality occurs, have an adverse effect on the subjects’ employability or economic status, insurability, social relationships, legal status, or psychological well-being. In addition, breaches of confidentiality can undermine the perceptions participants may have of the researcher or institution at which the study is conducted. Thus, the protection of subject data should be well considered by the researcher. As the IRB Guidebook notes, researchers usually seek informed consent from subjects in order to obtain information from them for research purposes. When informed consent has been obtained, there is little reason for concern about privacy. However, researchers are still expected to assure that appropriate confidentiality of research data is maintained. Privacy issues are more likely to arise when information is obtained for research purposes without the consent of subjects. For example, the majority of the complaints the University of Wisconsin–Madison IRBs have received from research subjects over the last 10 years, although these have been few, are related to perceptions that an individual’s privacy has been breached.

In their review of a research protocol, IRBs must ensure that subjects' privacy and the confidentiality of study data are adequately protected. Generally, the same levels of protections in place to help ensure the privacy of patients’ medical records are expected to be in effect for research records. In certain cases, such as when a potential breach of confidentiality could put subjects at significant legal, social, or economic risks, IRBs may require researchers to deidentify (anonymize) study data (ie, remove all direct or indirect identifiers from the data collected). If the data cannot be deidentified, an IRB may require an investigator to obtain a COC.

COCs are particularly warranted when the data being collected could be sought by others outside of the research study personnel and research oversight agencies, such as by law enforcement agencies that may subpoena the research data. Researchers obtain COCs from federal agencies that are under the auspices of the NIH, such as the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), or the National Institute of Mental Health (NIMH), which, in 1991, became components of NIH. COCs are generally granted when the research involves the collection of information relating to sexual attitudes, preferences, or practices; the use of alcohol, drugs, or other addictive products; illegal conduct; or an individual's psychological well-being or mental health. In addition, a COC would be warranted if the release of the information could reasonably be damaging to an individual’s financial standing, employability, or reputation within the community, or the disclosure of medical information could reasonably lead to social stigmatization or discrimination. There are other conditions in which COCs can be granted, such as in the case of tissue or data banks that are being maintained for unspecified future use.

Generally, IRBs will ask at least some of the following questions when assessing the adequacy of the measures in place to protect subject confidentiality:

- **Will the location of the data collection afford subjects adequate privacy?** Whether seeking medical information or conducting a survey, data should be collected in a setting that protects subject privacy to the greatest extent possible. For collection of particularly sensitive information, the IRB will expect additional safeguards to be in place, such as conducting an interview in a separate, secure room or ensuring that only a minimum number of study personnel are present.
- **Can the data collected be considered sensitive?** Data that may be considered sensitive include information about a stigmatizing medical condition, illegal behaviors (including illicit drug use), and some genetic information (eg, genes that suggest a person may be more susceptible to a particular disease or condition). The degree of sensitivity is affected by whether the data collected may be (or may be regarded as being) stigmatizing to specific subject populations.
- **How will the data be stored?** The IRB will want to know where collected data will be stored and what protections will be in place to ensure that personnel not involved in the research study do not have access to personally identifiable information.
- **How will data be recorded?** As part of its assessment, the IRB will consider whether recorded data will be anonymous or coded. If data are coded, the researcher should indicate where the code will be stored and who will have access to it. If identifiable data are recorded, researchers should state when the identifiers will be destroyed, as well as what measures are in place to separate direct from indirect identifiers. The investigator should also ensure that research personnel collecting or using directly identifiable data are knowledgeable regarding the confidentiality protections.
- **If medical or other private records will be accessed, do the researchers have valid access to**
them? Researchers planning on accessing private records should indicate whether they or other study personnel have valid access to those records. Depending on the type of records being accessed (eg, medical, school), other regulations besides the Common Rule may apply (eg, Health Insurance Portability and Accountability Act [HIPAA], Family Education Rights and Privacy Act [FERPA]).

- Do the consent forms, if applicable, adequately describe confidentiality protections and the potential risks, if any, of a breach of confidentiality? Consent forms should describe what measures are in place to protect subject confidentiality and be frank in describing any risk of breach of confidentiality. This is especially important for studies that are collecting sensitive data. Studies that have a COC must have appropriate language in the consent form describing the protections afforded by a COC, as well as its limitations.

Additional IRB Review Criteria: Safeguards for Vulnerable Subjects

Subject populations that are vulnerable to coercion or undue influence require special consideration by the IRB, as noted in the equitable selection of subjects and informed consent sections. Investigators who will enroll vulnerable groups in research, such as children, prisoners, mentally disabled people, or economically or educationally disadvantaged people, should explicitly describe what measures are in place to ensure that the subjects’ rights and welfare are adequately protected. Because the types of protections needed tend to be group- and protocol-specific, it is generally best to consult with the IRB office for advice of how to address this issue in the IRB application.

Tips for a Smooth IRB Review Process

Although some researchers may argue otherwise, the majority of IRBs consider themselves to be facilitators of ethically sound research that protects the rights and welfare of human subjects. When possible, prospective investigators (especially those new to the IRB review process) should discuss their project with an IRB representative for assistance in identifying and addressing potentially problematic issues before submitting it. In addition to consulting with their local IRB, the following general guidelines may assist researchers in providing IRBs with the information they need to make the required determinations and therefore provide for a smooth review process:

- Keep the requirements for IRB approval in mind. Investigators will assist their IRBs and themselves by creating research protocols and IRB applications that directly address the central requirements for IRB approval. In their research proposals to the IRB, researchers are in essence presenting an argument for the acceptability of their projects. Whether proposing an investigator-initiated study or adapting a multicenter protocol for conduct at a local site, researchers will almost certainly have more knowledge about the specifics of the study than individual IRB members. IRB applications differ significantly in their ability to draw out the study details essential to the review and approval of a study. As IRB members are typically expected to review numerous protocols at any given meeting, it should not be surprising that an IRB may miss study details that are relevant to a perceived problem, resulting in a potentially unnecessary modification requests. Researchers should become familiar with their IRB application process and consult with an IRB representative to ensure that they address any questions that typically arise for their type of research during the review process, as well as the essential IRB determinations.

- In consultation with the IRB, identify potential issues raised by a study and how the study either minimizes concerns or will address such problems. It is rare for a study to truly be without risk, and these risks are potentially not limited to the direct effects of interventions (eg, drug toxicities). Such concerns can involve privacy issues associated with the identification of the subject population, the identification of previously unknown clinical conditions as a result of study assessments, or the absence of standard of care treatment for the duration of a study. A robust plan to manage such issues will help to minimize IRB concerns.

- When creating an IRB application, consider the audience. IRB membership is not limited to medical professionals. An IRB must include nonscientists and community representatives. It is not uncommon for an IRB to include lawyers, philosophers, patient advocates, and statisticians. The acceptability of a proposed tradeoff between risks and benefits for any study is more than an assessment of sound medical or scientific research; it is also a moral determination. To the degree possible, limit the use of technical language and present information about the study in a context that can be understood by individuals without medical training.

- Preparing a good IRB application and protocol is time well spent. Provide accurate and sufficient detail to allow the IRB to approve your protocol. An IRB cannot approve absent or unclear information. If an application does not detail a safety monitoring plan, an IRB cannot make the requisite regulatory determination that the monitoring of data is sufficient to ensure the safety of subjects. If a proposal does not detail the protection of study data, an IRB
cannot determine that there are adequate provisions to protect the privacy of subjects and maintain confidentiality. An IRB can only approve what it receives. Although an absent questionnaire or unspecified control group (eg, eligibility criteria, procedures, recruitment plan) may involve minor risks compared with central study interventions, an IRB cannot make such an assumption and approve absent study components. Similarly, study documentation must accurately reflect what will occur. If inconsistent or unclear information is provided, then it would be unclear what an IRB was approving.

- **When seeking approval for the initiation of a multicenter study at your site, it is essential to describe how the protocol will be implemented locally.** This is particularly relevant to the description of subject identification and recruitment. Describe how the consent process will be conducted and who obtains informed consent. Indicate how the protocol differs from the institutional standard of care and what procedures would be performed to minimize risks locally that are not described in the sponsor protocol. Multicenter studies often allow for variation in study procedures. In the event of such potential variability, indicate the procedures that will be used locally and the rationale.

- **When in doubt, ask the IRB.** Even for minimal-risk studies, the IRB review process can be a confusing and complicated experience for researchers. IRB staff, chairs, and members can provide valuable guidance about the IRB review process and, in the vast majority of cases, are eager to do so. Researchers should not hesitate to contact their IRBs with questions or concerns regarding their studies. This may be particularly true when researchers are trying to determine whether their study even requires IRB review and, if so, what type of review to apply for (ie, exempt, expedited, or full) or when responding to requests from the IRB, which can sometimes be complex. Depending on an institution's policies, not all types of studies will need IRB review and approval. Policies regarding IRB review of quality assurance/quality improvement studies, program evaluation projects, and case reports vary among institutions, so researchers are encouraged to consult with their IRB to determine what type of IRB review, if any, may be required in these situations.

A quick call or e-mail to the IRB can save researchers time and effort, so when in doubt, investigators should consult with their IRB.

**Conclusion**

Even in the best of circumstances, the IRB review process can sometimes be frustrating and time consuming for both researchers and IRBs. Closer working relationships between researchers and their IRBs can help mitigate some of these frustrations and create a smoother and more efficient IRB review process for all. A central feature of this relationship is a better understanding of the requirements of IRB approval as delineated in the Common Rule. A more complete grasp of the determinations IRBs are required to make during the review process can greatly assist researchers in preparing applications that anticipate the questions IRBs are likely to raise during their deliberations and thereby avoid delays caused by deferrals or lengthy requests for additional information. Good lines of communication between researchers and their IRBs are critical not only to ensuring a smooth review process but also to protect the rights and welfare of human research participants.

**Additional Resources for Investigators**

**Federal**

- Certificates of Confidentiality Kiosk
- FDA Information Sheets
  - http://www.fda.gov/oc/ohrt/irbs/
- Investigator 101 CD-ROM
- Office for Human Research Protections IRB Guidebook
  - http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

**Selected IRB Websites Featuring Investigator Guidance**

- Duke University
  - http://irb.mc.duke.edu/
- Johns Hopkins University (School of Medicine)
  - http://irb.jhmi.edu/
- Stanford University
  - http://humansubjects.stanford.edu/
- University of California—San Francisco
  - http://www.research.ucsf.edu/chr/about/hsspWhatIsChr.asp
- University of Minnesota
  - http://www.research.umn.edu/irb/
- University of Pittsburgh
  - http://irb.pitt.edu/
- University of Wisconsin—Madison (School of Medicine and Public Health)

**References**


