

What every IRB member should know.

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## **Introduction**

The goal of this module is to help IRB members understand their unique and critical role in the protection of human subjects. Prerequisites for this module are the successful completion of all applicable modules of the CITI courses in biomedical and social behavioral tracts, and familiarity with the **Belmont Report**.

This module discusses important concepts about the IRB. The regulations guiding IRBs are purposefully vague, and how each institution complies with them is usually determined by its own policies and procedures. You should contact the IRB administrator at your institution for the specific information and requirements.

This module has four subparts:

- ▶ What to know before you join the IRB.
- ▶ The Human Studies Application.
- ▶ How IRB members review protocols.
- ▶ The IRB meeting.

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## **What to Know Before You Join the IRB**

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### **What Is the Institutional Review Board?**

The Institutional Review Board (IRB) is a committee mandated by federal law to protect the rights and welfare of human subjects participating in research activities. The law is specific to research conducted or supported by a federal department or agency. However, a majority of research institutions voluntarily apply this regulation (45 CFR 46) to all research conducted at their site, regardless of status or source of funding. The IRB achieves its primary function, protecting the rights and welfare of subjects participating in research, by educating researchers. An educated investigator makes the IRB's job easier.

Not all the individuals who comprise the board are experts in all the fields of research they review. However, as a whole, the membership should be fully capable of assessing the risks and benefits associated with a particular study, so that they can decide if the study is ethically and legally sound.

Educating researchers about the requirements assists them in complying with the regulations before problems occur. When compliance issues or problems occur, it is important to tell the investigator what the particular issue is, why it is a problem, and how to correct it. The investigator will likely learn from the experience and, hopefully, the problem will not reoccur in the future.

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## IRB Composition

In accordance with the Federal regulations, an IRB must be comprised of at least five members, at least one of whom is a non-scientist, one whose interest is scientific, and one member who is unaffiliated with the institution. One member can represent more than one role, such as a clergyman who may fill the roles of both the community (unaffiliated) member and non-scientist. Members must be diverse in race, gender and cultural background, and be sensitive to local community issues.



If an IRB receives research protocols in which the subjects are members of a vulnerable population (e.g., children, prisoners, the mentally handicapped), the IRB must have a member who is knowledgeable and experienced in working with the vulnerable population. Non-voting consultants may also be appointed to review research protocols that require expertise not represented on the IRB.

IRB members may not participate in the review of a research protocol in which they have an apparent or real conflict of interest (e.g., the IRB member or a family member is listed as an investigator on a protocol, or the IRB member is a major share holder in the sponsoring company of a reviewed protocol). Under these circumstances, the IRB member should recuse her or himself from the deliberations and not vote on that protocol.

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## Time Commitment

The scheduled time commitment required of IRB members is their attendance at convened **IRB meetings**, the length of which depends on the number and complexity of the projects to be discussed. In addition, members spend various amounts of time reviewing protocols in preparation for the meetings. Be sure you are fully aware of the realistic time commitment so that you can be a full participant in the IRB process.



Occasionally, IRB business may be conducted at times other than the convened IRB meeting. For example mail, telephone, or internal office procedures may be used to carry out expedited review of applications or application modifications. The acceptable turn-around time for your review depends on institutional

policies. You should check with the IRB Office or the IRB Chair to determine what will be expected of you.

Attendance at workshops or institutional training sessions, joining an IRB member listserv, and attendance at IRB professional meetings are excellent ways to stay current with international, federal, state and local regulations or institutional policy, and the best practices to be used to meet those regulatory or policy requirements. An educated IRB member is vital to ensure that the safety and welfare of human subjects are protected.

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## Liability of an IRB Member

Could you be sued or be held legally accountable for the decisions made by yourself or the IRB on which you serve? IRB members who serve at State Institutions are generally considered as serving a state function and are, therefore, covered by the state's insurance for employees. However, if you are at a state institution, private institution, or other organization, you should consult with the administrator of your IRB concerning the limits of your liability as well as institutional/organizational indemnification for your service to the Committee.

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## Role of the IRB Chair

The chair is an IRB member with voting rights equal to those of other members. Depending upon the institution, however, the chair may have added duties, such as reviewing adverse events, reviewing and signing all correspondence coming from the IRB, and handling initial triage of protocol violations. Regulations (45 CFR 46.110) empower the chairs (or experienced members designated by the chair) to conduct expedited review on certain categories of minimal risk research. The time commitment required of an IRB chair is significantly greater than that of the other IRB members.



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## Types of Review (Exempt, Expedited, Full Committee Review)

**Exempt studies** are research activities involving human subjects that are exempt from the federal regulations governing human subject protections. Exempt categories of research can be found in the CITI Module entitled "Basic Institutional Review Board (IRB) Regulations and Review Process" and in the [Code of Federal Regulations](#). The review for exemption is only for research determined to be within one of the exemption categories defined in 45 CFR 46.101. This level of review is often done by a member of the IRB Administrative Team.

The exemption status of research is determined by the IRB or other designated

institutional authority, not the investigator. Some Institutions may give an exempt study an approval date and a defined approval period for record keeping purposes. Other institutions may tell the investigator that the exempt study is approved indefinitely. The investigator must submit any study changes to the IRB. The IRB can then assess whether the exemption status for the project is still valid, or if the study now requires a different level of review (expedited or full committee). Some institutions choose to go beyond the regulations and use an expedited review process for any research that would otherwise fall under the exempt category.

**Expedited review** may be used for research that involves no more than minimal risk and is described in one of the federal expedited review categories, [21CFR56.110]. Expedited review means that one or more experienced members of the IRB (often the chair) can review the study without it being considered at a convened meeting. When conducting expedited review, the chair may exercise the same authority of a full IRB committee except he/she cannot disapprove the research study. (Review the CITI Module entitled "Basic Institutional Review Board (IRB) Regulations and Review Process" for details about the expedited review process.)

**Full Committee review** is required for the remainder of the study applications, for example, those with greater than minimal risk, or involving a vulnerable population. Studies can receive full IRB approval for a maximum of one year from the date of the last convened meeting when the protocol was reviewed.

- For example, the approval period for a protocol reviewed and approved at a convened meeting on January 10, 2005, can be 1/10/05-1/9/06. If non-significant modifications are required for this protocol, the investigator submits the revisions, and a final reviewer (IRB member) reviews and approves these changes. Regardless of the date the revisions are approved, the expiration remains January 9, 2006. (January 9, 2006 being one year from the last convened meeting at which the protocol was reviewed.)

### **The Human Studies Application**

#### **Initial Application for New Studies**

Depending on institutional requirements and the types of research being reviewed, you will likely see some or all of the following application elements.



**The initial IRB application** captures the general information about the study, including the name, status, and contact information for each of the investigators; funding sources, description of the study; and types of populations to be studied.

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Recommended components of an IRB application might include:

- ▶ Discussion of the scientific significance and goal of the study, including background and references.
- ▶ Description of the anticipated number of subjects to be recruited and the recruitment procedures.

- ▶ Discussion of the inclusion/exclusion criteria for subject entry or for use of data/tissues.
- ▶ Description of the potential risks and benefits to subjects, including issues of confidentiality and other ethical problems, and procedures for minimizing the risks.
- ▶ Identification of the vulnerable groups that may be encountered in the subject population, with emphasis on additional protections that will be put into place to ensure that the rights and welfare of such groups are protected.
- ▶ Discussion of how the capacity to consent will be assessed for all subjects.

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Components of the IRB application might also include:

- ▶ The **consent forms** for adult subjects, **permission forms** for parents of minor subjects, and **assent forms** for minor subjects (in most states this is younger than 18 years old). The IRB may approve a consent procedure that does not include or that alters some of the elements of informed consent. For example, the IRB may waive the requirement to obtain a signed consent form when the consent document is the only link between the subject and the research, and the principal risk of harm would come from a breach of confidentiality. In place of a signed consent form, the IRB may require the researcher to provide a written statement regarding the research in the form of an information or fact sheet . (See "General requirements for informed consent", [45 CFR 46.116](#) ; "Documentation of Informed Consent", [45 CFR 46.117](#) for more details.)
- ▶ Copies of all **interviews, surveys, questionnaires**, and other research instruments.
- ▶ All **recruitment materials** to be used, in any media (e.g., letters, printed ads, TV or radio commercials, and email solicitations).
- ▶ **Grant proposals** submitted to federal (e.g., National Institutes of Health, National Science Foundation) or private (e.g., American Heart Association) sponsor.
- ▶ **An experimental drug/device protocol from an industry sponsor**, normally tested at multiple sites (i.e., a multi-site clinical trial). Usually, the IRB will require a lay summary of the grant application or industry drug/device protocol to distribute to board members. Some IRBs have adopted an alternative of providing the full study protocol only to primary and secondary reviewers.
- ▶ **Investigator brochure(s)**, which describe, in detail, all the information known about an experimental, non-FDA-approved drug, including its chemical properties, pharmacological properties, and history of use in animal subjects and human subjects to date.
- ▶ **Package insert(s)** for each FDA-approved drug being used off-label or for any FDA-approved drug specifically being investigated in the study protocol. This is the information sheet found in many of the drugs purchased over the counter or through a pharmacist, or in magazine drug

advertisements that describe indications, contraindications, side effects, etc. of the drug.

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## The IRB Continuing Review Application

Federal regulations require human subjects research protocols to be reviewed a minimum of once per year (21 CFR 56.109 and 45 CFR 46). Depending on institutional requirements and the types of research being conducted, IRB members are likely to see some or all of the following Continuing Review Application elements.



The IRB Continuing Review Application will likely incorporate:

- ▶ A general progress report on the study's activities over the past approval period, including: the number of subjects enrolled, withdrawn, and removed; a summary of any changes requested and/or approved; and a report of any unanticipated problems that were reported to the IRB.
- ▶ **Consent, permission, and assent forms** proposed for use in the upcoming approval period.
- ▶ The **full study protocol** (If a primary/secondary reviewer system is used only the primary/secondary reviewers will receive the full copy of the study application; all others may receive a study summary).

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## How IRB Members Review Protocols

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### Weighing Risk and Benefit

An important function of IRB members is to assess the potential risks and benefits of a particular study based on the three principles of the Belmont Report—Respect for Persons, Beneficence, and Justice. It is important to determine if the "ratio" of risk to benefit is reasonable, given the goals of the study. Many variables can affect this assessment, including the proposed subject populations, proposed procedures, and scientific background supporting the study. In order for a study to obtain approval, the IRB must determine that it is within the ethical guidelines as outlined in the Belmont Report while also ensuring that it meets the federally mandated criteria for approval. These criteria are available for review at 45 CFR 46.111 and, where applicable, 21 CFR 50.111

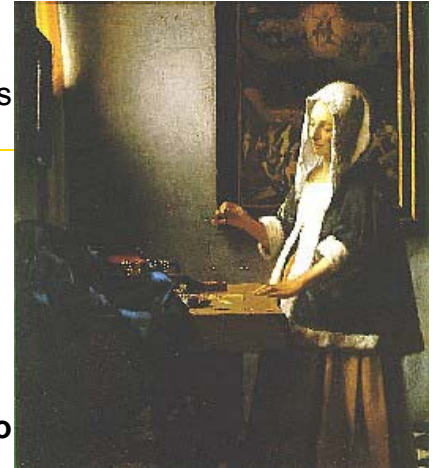
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## Reviewing New Applications

To ensure meaningful and efficient deliberations, IRB members should be familiar with the submitted applications. Where a lay summary of the IRB application is used, all Committee members should review it prior to the convened meeting. Primary and secondary reviewers should review the full protocol thoroughly.

When reviewing a proposal, the goals are to:

- ▶ Identify the procedures being conducted solely for research purposes.
- ▶ **Identify the risks** involved in the study (e.g., physical, psychological, legal, and social).
- ▶ **Identify how the risks are minimized.**
- ▶ **Assess whether the risks are reasonable in relation to the anticipated benefits and, if the risk is more than minimal, assess whether the benefits outweigh or are in-balance with the risks.**
- ▶ **Assess the adequacy of the privacy and confidentiality procedures.** For example, if the investigator is conducting studies on a sensitive topic, such as spousal abuse or illegal drug use, have precautions been taken to protect the identity and confidentiality of the participants?
- ▶ **Assess, when appropriate, that the study addresses how the data will be monitored to ensure the safety of enrolled subjects.** For example, do the investigators propose to have an independent, 'real time' analysis of the data performed to assess if subjects in one treatment arm are responding significantly better or worse than the other? Or, perhaps the study's risk/benefit analysis is acceptable for approval, but the IRB would feel more comfortable reviewing the data themselves after a certain period of time, or after a certain # of subjects has been run.
- ▶ **Determine if subject selection is equitable.**
  - Has the investigator used appropriate inclusion and exclusion criteria?
  - Does the study target the appropriate population? Populations of convenience should be avoided. For example, investigators should not target a population just because of "easy access," or a population that will not benefit from the research, whether individually or as a social group.
  - Is the selection free of coercion? Is there an authoritative relationship between the person who is recruiting and the potential participant, such as teacher/student, physician/patient, and employer/employee? Have procedures been put into place to minimize possible coercion?
- ▶ **Read the consent documents** thoroughly and confirm that they are consistent with the protocol.
  - Are research procedures and associated risks addressed in the consent form?
  - Is the form written in a language suitable for the prospective participants?
  - Can you clearly describe the study after reading the form?
  - For studies involving medical treatments, can you tell what part is standard care and what part is research?
  - Are there any statements that appear to be coercive or give the appearance that the subject is waiving her or his legal rights?



Are the procedures written in the order of occurrence?

Is there consistent use of the terms "subject" or "participant"?

- ▶ **Check and make sure all sections** of the application are included in the packet and are completed correctly.
- ▶ **If vulnerable populations will be enrolled**, do the investigators address additional protections for these subjects?

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### Reviewing Continuation Applications (Continuing Review)

The IRB is federally mandated to conduct an overall assessment of the research study, at a maximum of one year intervals, and reassess whether or not the research meets all the required elements for approval [45 CFR 46.109.e]. This decision is based on all the information that is available about the conduct of the study since the last time it was reviewed and approved. The continuing review should be a cumulative review of any changes that may have occurred in the study within the last year, including adverse events, amendments (revisions, changes, or modifications), and any unanticipated problems. In addition, the review may include the relevance of any new federal mandates or institutional policies, which may alter the way the study is conducted, the way the consent documents are written, or how the study's risk/benefit ratio is determined.

The Continuing Review must establish that the number of actual subjects enrolled into the study is equal to or less than the number of participants described in the approved protocol. The only possible exceptions to this strict accounting for numbers are in multi-site pilot studies, or clinical trials, where the overall target enrollment number may be used as the reference, depending on local requirements (check your institutional policies for these requirements).

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### Amendments (Revisions, Changes, or Modifications) to an Approved Study

The IRB must review and approve all amendments to study protocols **before** the researchers can implement them. The process of amendment approval follows the regulatory guidelines:

- ▶ The IRB needs to determine if the modification is reasonable given the overall study design, and if the level of risk known about the study has changed.
- ▶ Amendments are reviewed the same way a new study is reviewed, that is, by the convened IRB or by expedited review, depending on how the changes affect the protocol.
- ▶ Minor modifications—those changes that are minimal risk and do not significantly alter the risk/benefits balance or other study elements—may be reviewed under the expedited review process.
- ▶ Major modifications, requiring full IRB review, are those that might increase the risk to participants or otherwise represent a substantive change, such as the inclusion of a vulnerable population, or change in treatment.

When reviewing a proposed amendment, IRB members must assess if the subjects need to be made aware of the new information. The consent form may need to be revised and/or a

consent addendum may be needed to inform those who are already enrolled in the study of the new information. If the investigator has included a revised consent form, it should be reviewed against the information provided with the amendment, to ensure the consent form is accurate.

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### **Unanticipated Problems (Including Serious Adverse Events)**

The IRB depends on the investigator to report promptly any unanticipated problems involving risks to subjects or others, including any serious adverse events. In reviewing the reported event, the IRB must assess the relationship of each problem or event to the subjects' overall participation in the study, as these may affect the risk/benefit ratio. As a result of the assessment, the IRB may determine that the study protocol and/or consent forms need to be modified, and/or currently enrolled subjects need to be informed of the new information, or that the study must be stopped.

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### **The IRB Meeting**

#### **Receipt of Agenda and Review Materials**

Generally, one week in advance of a convened meeting, IRB members receive the meeting agenda and materials to be reviewed. The agenda lists protocols to be reviewed at the meeting and includes the detailed application submission materials for those research protocols. The list of protocols includes continuing review applications ("renewals"), new research protocols, and studies proposing major amendments or reporting adverse events requiring full Committee review.



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#### **The Quest for a Quorum**

Regulations require that a majority of IRB members must be present to discuss and vote on agenda items submitted under the category of Full Review of research protocols. A quorum consists of a majority of total number of IRB voting members identified on the official committee roster (e.g., a quorum for a 10-member or 11-member review board is 6 voting members). In order for the Committee to conduct the review and to vote a convened IRB is federally required to include one member who is a non-scientist [\[45 CFR 46.108\(b\)\]](#) in the quorum.

If an IRB member must recuse himself or herself from the deliberations and the vote of a particular protocol, the IRB chair and/or staff must assess the status of the quorum. If quorum is lost, the protocol cannot be reviewed at that IRB meeting.

An IRB may include alternates for specific board members. This enables IRB members to share the workload associated with membership. However, if a member and his or her alternate are both present at the same meeting, only one may vote on each protocol. In

addition, the shared position will count as one member toward the quorum needed for full Committee actions.

Given the importance of having a quorum for an IRB to conduct business, it is vital that a member inform the IRB staff as far in advance as possible if he or she will be unable to attend a particular meeting or if there is a conflict of interest for a specific protocol requiring recusal of the voting member from the meeting's discussion and vote.

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### **Quorum Confirmed, Committee Work Begins!**

In addition to reviewing protocols, the IRB may have other business to conduct at the convened meeting. This may include approving the minutes of the last convened meeting, bringing reports to the Committee's attention, summarizing approved exempt or expedited studies, and reporting on studies previously reviewed by the full Committee that were subsequently approved by a final reviewer or subgroup of reviewers. The materials pertaining to this other business may be in the package sent beforehand or it may be available at the meeting.



Some IRBs use a primary reviewer system in which one or more members are assigned (in advance) to present the protocol for discussion at the convened meeting. The primary reviewer (and secondary reviewers, when used) is expected to begin the deliberations on a particular research study by:

- ▶ Providing the IRB with a brief overview of the research being reviewed.
- ▶ Identifying major concerns arising in the project, perhaps involving the risk/benefit ratio, the method for obtaining informed consent, or subject selection.

After completing deliberations there is a call for the Committee to vote on the study. There are a limited number of actions that an IRB Committee can take under the governing Federal regulations [45 CR 46.109](#). A majority vote of the IRB Committee members present at the meeting decides the action. The acceptable actions are:

1. **Approved as Submitted.**
2. **Modifications Required.** In this situation, the study is approved in principle at the convened meeting. However, the Committee requires further minor or minimal risk study change(s) prior to final IRB approval and study activation. The Committee's requested changes need to be explicitly communicated to the investigator, in writing, with appropriate rationale. An investigator's response to these Committee specified

changes may be reviewed under an IRB expedited review process. If the Chair or designated IRB member conducting expedited review of the investigator's response is satisfied that all Committee specified changes were incorporated, the IRB office may then route all final approval documents to the investigator and accrual may be initiated. The IRB meeting minutes should note that the Committee agreed with this approach and did not require resubmission for full board review provided the investigator agreed and implemented the changes specified by the Committee.

3. **Disapproval of New Studies:** The study is disapproved. Reasons for taking this action may include the following:

- ▶ The Committee has concerns with study procedures that are greater than minimal risk. In this situation the Committee may request additional information regarding risk minimization or alternatives that would permit a complete risk: benefit assessment.
- ▶ The scientific design or validity is questioned by the IRB. The Committee may request additional sample size clarification; stopping rule parameters; or consulting expert opinions for review before approving the study. This information is necessary as the IRB may only approve studies that have sound research design.
- ▶ If a study is submitted to the IRB with numerous typographical errors, language that is too technical throughout a consent document or inconsistencies across study documents (e.g., the IRB application, protocol and consent form each describe differing age ranges, accrual goals or dosages of a medication ) then resubmission and correction prior to re-review by the full board is required.



The Committee is required to notify the Investigator, in writing, the decision to disapprove the research application as well as the justification for reaching the decision. The Investigator is permitted a chance to respond to the Committee's action and concerns either in person or in writing.

Many IRBs also adopt procedures that allow them to table or defer a study if the Committee runs out of time or a quorum has been lost. The study would then be reconsidered at the next full board meeting. Please check with your IRB administrator for the specific policies of your institution.

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### Reviewing the Meeting Minutes

The minutes from an IRB meeting must be approved (accepted) at the next convened IRB meeting by a majority vote of the membership. They should be read carefully and specifically checked for accuracy and completeness. Several best practices are:

- ▶ A good check on the accuracy of the minutes is to pay particular attention to the

sections that describe the Committee deliberations and findings of studies for which you were the primary or secondary reviewer. You are likely to remember those protocols the best, as well as the issues that were raised during the deliberations.

- ▶ Review the details in the minutes for studies where the Committee had ethical or legal problems to consider, or where there were vulnerable populations that required the IRB to consider additional protections.
- ▶ Look for protocols where you were an investigator and had to recuse yourself. Is the vote count correct, marking you as not voting?
- ▶ All descriptions of discussions that took place at the meeting should be reviewed for accuracy and completeness.

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### **Confidentiality and the IRB Member**

IRB members and staff are required to keep confidential the proceedings of an IRB meeting, including any specific details regarding the studies reviewed. However, depending on an Institution's policies, a single IRB member may contact an investigator prior to the IRB meeting and ask questions or seek clarification about the submitted application. An IRB chair, or IRB member at the request of the IRB chair and Committee, may be asked to consult with an investigator regarding specific concerns raised in the IRB meeting.

IRB members and staff generally do not disclose, to an investigator, the identity of a primary or secondary reviewer assigned to his or her protocol as the decision about a study is based on all IRB members' deliberation and vote.

In many institutions, IRB members and staff sign a confidentiality agreement. Typically, individuals not on the IRB who attend a meeting, (e.g. expert consultants, students/study staff wanting to observe and learn more about the IRB process) sign a confidentiality agreement at the outset of the meeting.



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### **Summary**

The purpose of the IRB is to protect the rights and welfare of human research subjects. This common goal can be accomplished through many different avenues including, but not limited to, by advising researchers how to design their studies so as to minimize potential harm, by reviewing research prior to its initiation to ensure that it meets established criteria for the protection of human subjects, by assessing researchers' requests for amendments to their research protocol, and by monitoring how approved research is conducted.

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IRB members ensure that the rights and welfare of human subjects are paramount in the research process, and that the highest standards of ethical conduct are employed in all human subjects research.

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