# Chapter 10. An institutional review board (IRB) application

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*"Somewhere, something incredible is waiting to be known." – Carl Sagan*

Objective: To describe the purpose of and IRB and a general approach to completing an IRB-approved research project.

## What is an IRB?

Human subject research has led to what we know about the current practice of medicine and is the reason that medicine has evolved so dramatically over time. An Institutional Review Board (IRB) is a committee established to protect human research subjects. An IRB must review and approve any federally funded or regulated research that involves human subjects to ensure the rights and welfare of those human subjects is protected, and most institutions require IRB approval for any research. According to federal regulations, an IRB has the authority to approve research, disapprove research, modify research, conduct continuing reviews, observe/verify changes, suspend or terminate approval, and observe the consent process and research procedures.

An IRB is made up of at least 5 members which includes members of both sexes. The members should have varied professional backgrounds. At least one member should be from a nonscientific area, one member from a scientific area, and one member with no affiliation with the organization. When research is being reviewed that includes vulnerable populations, there should be inclusion of an individual with an understanding of the vulnerable population being studied.

## Why do we have IRBs?

*"Atrocities are not less atrocities when they occur in laboratories and are called medical research." – George Bernard Shaw*

A discussion of IRBs and their role in the protection of human subjects of research would be incomplete without an understanding of some key ethical principles and a brief history of human subject research. Vaccination trials in the 1700s were some of the first human subject experiments to be documented. Research was conducted on humans with no oversight, often putting human at significant risk for minimal prospective gain. Although there were some calls for better human research oversight from the medical community, widespread understanding and demand for human subject protection did not occur until World War II, when Nazi doctors and scientists were put on trial for murder in Nuremberg. Ten key elements for conducting human

research were included in the legal judgement and sentences handed down at the trial, known as the Nuremburg Code.

However, there remained little formal oversight of human subject research, which was often conducted on the most vulnerable populations. Dr. Henry Beecher wrote an article for the New England Journal of Medicine in 1966 which brought to light some research studies conducted by reputable researchers and published in major journals that were governed by controversial ethics. With the Beecher article, the public became increasingly aware of the ethics of research.

One of the most controversial human subject studies, and the one that was most influential in leading to governmental change, was the Public Health Service (PHS) Syphilis Study. The study included hundreds of men with and without syphilis and was begun before there was a known treatment for syphilis. These men were followed over time and subject to unnecessary testing, including spinal taps. Penicillin was found to be an effective treatment for syphilis in the 1940s but these men were denied antibiotic treatment and the study continued to track them until 1972, when it first appeared in the national press.

Congress subsequently formed a panel which immediately stopped the study but also recommended the design and implementation of federal regulations to protect human subjects in future research. Human research in the United States is now governed by 45 Code of Federal Regulations 46. Through the authorization of Congress, the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research was formed in 1974. In 1979 the National Commission published the Belmont Report which identifies three basic principles that underlie all human subject research – respect of persons, beneficence, and justice. These ethical principles are what guide the evaluation of a study by the IRB.

**What are the different types of IRB review?**

There are three different types of IRB review: full committee review, expedited review, and review for exemption status. A full review requires that a quorum of IRB members be present at a convened meeting to review the application. The members present must include a nonscientific member and should also include a physician. For approval, a majority of the members present must approve the research. The IRB can decide to approve, modify, or disapprove of the research presented. Disapproval is typically done because the IRB does not believe a project is feasible or that it violates an ethical principle. If your project is disapproved, set up a meeting with the IRB Chair to discuss the reasons and to determine if the objections can be overcome.

The expedited IRB review process can be used for research involving no more than minimal risk to subjects or when the research project is done in specific, federally defined categories. Table 1 delineates the seven categories for a new expedited review. An expedited review can be performed by the IRB chair or one or more experienced IRB members designated by the chair. The reviewer(s) can approve the research, require modifications, or refer to the full IRB meeting; they may not disapprove the research.

The exempt IRB review process can be used for research that involves no human subject risk and is exempt from the other provisions of the regulations. Table 2 outlines the six categories of research that is eligible for exemption status.

**What do I do if I think I have a good research project that would require IRB approval?**

Starting an IRB research project can be a daunting task, but as with many aspects of research, the most difficult part of completing a research project is getting started. Once you have a framework for a good study you should start writing the IRB application. Each institution has a unique IRB application form, but all of them will include the following sections: objective of the study, review of the literature to date (which may help better refine the study framework), and a basic description of the research design. The how-to guide below includes the common elements required for an IRB application.

Contact your local IRB or research coordinator to better understand the process of routing an IRB application. You may find that your local IRB has specific/unique requirements that are helpful to understand before completing the application. Also, be sure to collaborate with colleagues. Research projects requiring IRB approval can be labor and time intensive so find others with similar interests/passions to help share the work. Many organizations also have employees specifically tasked to help with research applications. If not, you may be able to find someone who has been through the process before and can help mentor you along the way.

Do not get discouraged! Your IRB application is likely going to be returned requiring modifications at least once. Start the process with that as an expectation, and use the comments made by the IRB to improve your project. Keep in mind that many of the IRB members have extensive research experience.

**Summary**

Doing an IRB research project can be a daunting task; consider starting with IRB exempt or expedited research projects. Build on early successes and learn from failures.

Summary Points

- Human subject research is the backbone of our continuously evolving medical practice and IRBs are an essential part of this process – to ensure that the rights of those human subjects are protected.
- An IRB can decide to approve, modify, or disapprove of a research study.
- Depending on the risk to human subjects, IRB review can be exempt, expedited, or require full review.
- Institutions often have unique IRB applications although they all include common elements – objective of the study, background (review of the literature to date), and a basic description of the research design.

**Table 1: Expedited IRB categories**

| Category | Description |
|---|---|
| 1 | Studies on drugs or medical devices for which an investigational new drug (IND) application or investigational device exemption (IDE) is not required<br><br>Studies with a cleared/approved medical device that is being used in accordance with its approved labeling |
| 2 | Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture |
| 3 | Prospective collection of biological specimens for research purposes by noninvasive means |
| 4 | Collection of data through noninvasive procedures routinely employed in clinical practice (with some qualifications) |
| 5 | Research involving data, documents, records, or specimens that have been collected, or will be collected solely for nonresearch purposes |
| 6 | Collection of data from voice, video, digital, or image recording made for research purposes |
| 7 | Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies |

Protection of Human Subjects, 45 C.F.R 46. 2009.

**Table 2: Exempt IRB categories**

| Category | Description |
|---|---|
| 1 | Research conducted in established or commonly accepted educational settings, involving normal educational practices |
| 2 | Research involving educational tests, survey procedures, interview procedures, or observation of public behavior unless the information is recorded in a way that the subjects can be identified and disclosure of responses could reasonably place the subjects at risk of criminal or civil liability or be damaging to their financial standing, employability, or reputation |

| | |
|---|---|
| 3 | Research involving educational tests, survey procedures, interview procedures, or observation of public behavior not exempt as above, if the human subjects are elected or appointed public officials or if federal statute requires without exception the confidentiality of the identifiable information |
| 4 | Research involving the collection or study of existing data if these sources are publically available or the information is de-identified |
| 5 | Research and demonstration projects conducted by heads of government departments or agencies designed to study, evaluate, or examine multiple aspects of public benefit or service programs |
| 6 | Taste and food quality evaluation and consumer acceptance studies |

Protection of Human Subjects, 45 C.F.R 46. 2009.

**References:**

1. Protection of Human Subjects, 45 C.F.R 46. 2009.

2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. Bethesda, Md.: The Commission, 1978.

3. Beecher HK. Ethics and clinical research. N Engl J Med. 1966;274(24):1354-1360.

**How to write an IRB**

*For this recipe you will need;*

- *An idea for a research project*
- *Your institution's IRB application*
- *Patience, perseverance, and ideally an experienced mentor!*

**Step 1:** Clearly define the question(s) your research seeks to answer.

**Step 2:** Tell your colleagues about your project and solicit assistant investigators.

**Step 3:** Clearly identify roles, responsibilities, and timeline expectations with your co-investigators, including anticipated author order on the paper you will write to publish your findings. Put this in writing and make sure everyone has a copy.

**Step 4:** Complete this research outline (easiest to break it up into parts among your group):

**Title:** Be concise, don't capitalize every word

**Subject Population:** a brief description

**Age of Subjects:** Specify in particular the follow age ranges: newborns, 0-17, 18-65, over 65

**Collection of Subject Demographics:** What are you collecting? I.e., ages, gender and race

**Population:** Who are you studying?

**Does the project involve active subject recruitment?** If you'll recruit subjects, you'll need to describe in detail how you will do this.

**Control / experimental / total subjects:** Describe each group.

**Abstract:** This gives the IRB a good idea of what you are trying to study and how you plan to go about it. Put effort into this – with minimal modification this is the abstract to the article you'll publish about this project!

**Research Plan:** This is where you build a detailed outline of your project

**1. Objectives / Specific Aims** What clinical question are you trying to answer? What is your null hypothesis?

**2. Background and Significance** Why is this important? To whom is it important?

**3. Research Design / Methods / Subject Justification** Specify your research design. Is it retro- or prospective? How many arms? Cross over? Briefly describe your methods (you'll go into detail later). Will you pull data from an established database? Recruit subjects? Give a justification for your subject selection. This is particularly important if your subjects are considered vulnerable populations.

**a. General Approach**

**i. Research Objective** What clinical question are you trying to answer? What is your null hypothesis?

**ii. Detail how many groups or Arms are in the Study and what each receives** Be complete and concise.

**iii. Randomization procedures** How will you randomize? If you are not randomizing, why not?

**b. Methods and materials** Again, complete and concise. Be sure to include all actions the researchers will take, all anticipated interactions with subjects, and all tools/surveys/equipment you plan to use.

**i. Experimental Procedure** Step by step, what are you planning to do?

**ii. If collaborative, what occurs at each institution** Be explicit. Your IRB may require a formal data-sharing agreement or memorandum of understanding.

**iii. Research material to be collected** Be concise and complete. Anything not listed to the IRB cannot later be collected (unless you later submit and receive approval for a waiver before you collect it.) Here you can also specify PII vs non-PII data. Studies without PII may be eligible for an "expedited" review.

**iv. Data collection tools** Forms, surveys, databases, equipment etc.

**v. Protection and security of data and identifying information** Physically or electronically how will information be secured and who will have access to it?

**vi. Disposition of data and identifying information at end of project** Be specific – for how many years will information be retained. How will physical and electronic information be destroyed or archived?

**vii. Gender and ethnicity** Will this information be collected and if so, why?

**c. Subject population**

**i. Subject inclusion and selection criteria** How will you identify appropriate subjects for inclusion?

**ii. Subject exclusion** What, if any, are your exclusion criteria?

**iii. Subject recruiting methods** Be thorough – signs, mailers, booths, commercials, emails? Be explicit in subject compensation if any – money, time, promotional items. Your recruiting materials will be reviewed and should clearly address how the study might (or, better, will not) impact the subjects' access to care or quality of care.

**iv. Informed consent procedures** Be thorough, and be sure to address potential barriers like language, legal ability to consent, subjects' ability to revoke consent (your consent forms should include instructions on how to revoke consent), and again address how the study might (or, better, will not) impact the subjects' access to care or quality of care

**v. Justification for use of this subject population** The more vulnerable your subjects, the more potential harm of your intervention, the stronger your justification must be.

**vi. Vulnerable populations** Clearly identify all "vulnerable" subjects. Vulnerable populations explicitly include: children, minors, pregnant women, fetuses, human in vitro fertilization, prisoners, employees, military persons, students in hierarchical organizations, terminally ill, comatose, physically and/or intellectually challenged individuals, visual or hearing impaired, ethnic minorities, refuges, international research, economically and disabled and healthy volunteers. Vulnerable populations also include *any other* population that might be at risk for exploitation.

**vii. Number of subjects and justification** Justification comes from your statistical modeling – this allows the IRB to see that you are not subjecting an unnecessary number of subjects to your intervention.

**i. List and document risks** Be broad – if data you collect (including that the subject is involved in your study) were available to all persons, what might happen? Loss of insurance? Loss of job? Embarrassment? If the intervention or lack of intervention were to cause harm, what would that harm be? Side effects? Loss of function(s) permanently or temporarily? What are the chances of harm with your intervention – are there animal studies, previous human trials, theoretical models, analogous interventions that allow estimation? Don't forget every aspect of your intervention. For example, treatment with intramuscular agent X includes not only the effects of X, but the risk of injection alone.

**ii. Justification of risks** What might subjects in particular and the field of medicine in general gain?

**iii. Minimization of risks** Be thorough – address every risk listed above and clearly describe risk minimization process and procedures. This includes pre-screening subjects, intervention technique, and post-intervention monitoring.

**e. Benefits** What does the world gain from this study?

**f. Cost to subjects** Typically time and money, but also may be physical limitations (including driving, reading, sports) or mental limitations (fatigue, focus) depending on your interventions.

**4. Adverse event management and reporting** The next step to risk mitigation strategies above. If something goes wrong, what happens? Describe how an adverse event would be identified, to whom it would be reported, and what possible outcomes an event might trigger – risk amelioration, dropped from study, study on hold, study shut down, anything else. Also note that this must include how the researchers will notify the IRB.

**5. Statistical analysis** What analysis will you perform? Why? Make sure your model fits your anticipated data. Describe in detail power, confidence intervals, and sample sizes. Consider the impact of smaller sample sizes/drop-outs on your confidence intervals.

**6. Significance to your institution** Some institutions will explicitly ask this. It is a way for their IRB and internal leadership to make sure researchers are meeting the needs of their employers.

**7. Patent disclosures/inventions** Are you testing for your patent or invention? Disclose here.

**8. Potential hazards to the research team** Detail.

**9. Anticipated enrollment time** Include an estimate of how many subject per year over how many years your study will run.

**10. Bibliography for background section/ research plan** Some IRBs will direct you to cite in a specific style. You should have a great bibliography – See Chapter 3 for how to do a literature search. Be thorough – this will be the foundation for the References in the article you'll publish about this project.

**Step 5:** Cut and paste from the outline into your institution's IRB form.

**Step 6:** Submit your IRB!