AN IN-DEPTH LOOK AT THE INSTITUTIONAL REVIEW BOARD (IRB)

The Institutional Review Board (IRB) is a local administrative body established in response to the National Research Act of 1974 to protect the rights and welfare of human subjects recruited to participate in biomedical or behavioral research activities. All human subjects research conducted under the auspices of Brandeis University or by a member of the Brandeis University community must be reviewed and approved by the Brandeis University IRB.

Defining Human Subjects Research
For a project to require IRB review, it must 1) constitute research, and 2) involve human subjects, as defined by the Federal regulations:

Research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

Human Subject: A living individual about whom an investigator conducting research:

1. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens
   — or —
2. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

Further helpful definitions:

Systematic Investigation: A project that methodically tests (quantitatively or qualitatively) a hypothesis or research question, by gathering and analyzing data with the intention of drawing conclusions

Generalizable Knowledge: Data designed to apply to a population beyond the research subjects themselves and contribute to current academic understanding

About Whom: Refers to information the subject discloses about him/herself (including his/her opinions), as opposed to information/facts the subject shares regarding an external topic (such as a program, product, or procedures) about which the subject can be considered an expert

Intervention: Physical procedures by which data are gathered, and manipulations of the subject or the subject's environment that are performed for research purposes

Interaction: Communication or interpersonal contact between investigator and subject

Identifiable: The identity of the subject is or may readily be ascertained by the investigator or associated with the information

Private Information: Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public

Some activities that the federal regulations specifically deem not to be research include scholarly and journalistic activities, including the collection and use of information, that focus directly on the specific individual about whom the information is collected. Examples include: Oral history, journalism, biography, literary criticism, legal research, and historical scholarship.
History
In 1946-47, 23 medical doctors and administrators were tried in Nuremberg, Germany for conducting human experimentation on prisoners of Nazi concentration camps during World War II. Dr. Leo Alexander, a key medical advisor during the trial, submitted ten ethical principles for research to the Counsel for War Crimes by which to try the defendants. The Counsel adopted these principles, which became known as the Nuremberg Code. The principles covered such things as voluntary consent, benefit-risk analysis, freedom of subjects to withdraw, and qualifications of the investigator.

In the 1950s, while attempting to develop an anticonvulsive drug, the West German company Chemie Grünenthal GmbH found that the drug they had been testing had tranquilizing effects without the danger of death from overdose, as well as anti-nausea properties for pregnant women experiencing morning sickness. In 1956 the drug Thalidomide was licensed for over-the-counter sale in Europe and Asia. The drug did not undergo rigorous clinical testing, however, and in 1961 a link between Thalidomide and birth defects became clear. Though the drug was never approved for use in the United States, as a result of the publicity, Congress enacted the Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act, mandating stricter FDA regulatory review of new drugs.

In 1964 the World Medical Association (WMA) issued ethical guidelines for the regulation of clinical medical research and protection of research subjects in the Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects. For the first time, the Declaration discussed the concept of an ethics review board to help guide the investigator.

From 1932-1972, the US Public Health Service enrolled 400 low-income African-American males with syphilis in a research project, dubbed the Tuskegee Study, to study the effects of untreated syphilis. While the men were told they were being treated for “bad blood” (the term used at that time to describe a number of ailments including anemia and fatigue, as well as syphilis), in fact, they were not: treatment was withheld throughout the study, despite the advent of penicillin and “Rapid Treatment Centers” to treat syphilis in the 1940s. In 1968 concerns were raised about the ethics of the study, however the Centers for Disease Control and Prevention (CDC), American Medical Association (AMA), and National Medical Association (NMA) continued to support the study. In 1972 the Associated Press ran a story about the Tuskegee study and the study was ended as a result of the publicity.

In 1974, as a result of the publicizaion of the Tuskegee Study, the National Research Act was passed, which called for the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to develop ethical guidelines for human subjects research. The result was the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, published in 1978.

Guiding Principles and the Regulations
Drawing on principles discussed in the Nuremberg Code and the Declaration of Helsinki, the Belmont Report serves as the ethical framework for the protection of human subjects and discusses three fundamental principles by which human subjects research has since been guided:

1. Respect for persons, or treating individuals as autonomous agents (“capable of deliberation about personal goals and of acting under the direction of such deliberation”) and protecting persons with diminished autonomy

2. Beneficence, or protecting individuals from harm by maximizing potential benefits and minimizing potential for harm (risk)

3. Justice, or distributing the risks and potential benefits of research equally among those who may benefit from the research
The Federal regulations, which established and guide the IRB, were first published in 1974 in 45 CFR 46, extensively revised as a result of the Belmont Report, and revised again in 2018. The regulations include five parts:

- **Subpart A**: Basic HHS policy for the protection of human research subjects
- **Subpart B**: Additional protections for pregnant women, human fetuses and neonates involved in research
- **Subpart C**: Additional protections pertaining to biomedical and behavioral research involving prisoners as subjects
- **Subpart D**: Additional protections for children involved as subjects in research
- **Subpart E**: Registration of Institutional Review Boards

Subpart A of the regulations – known as the Common Rule for its codification by 15 Federal departments and agencies – transforms the three principles of ethical research discussed in the *Belmont Report* into well-defined protocols, and outlines the functions and operations of the IRB and criteria for IRB approval of research. Subparts B-D are concerned with the welfare of what the regulations refer to as vulnerable populations and outlines additional provisions that must be followed when using these populations as research subjects. Subpart E discusses the administrative details of the IRB.

**Respect for Persons**

Of the *Belmont Report*’s three ethical principles operationalized by the regulations, respect for persons gets the most attention. The cornerstone of this principle is the informed consent process; for to treat a subject as an autonomous agent, one must give that subject the opportunity to make a choice to act based on the facts of the research and his/her own beliefs and values. Throughout the historical research discussed above, we see a pattern of subjects being treated as non-autonomous agents:

- The opportunity for consent was withheld from the victims of the Nazi experiments. (Subjects were held captive and powerless in the concentration camps with no ability to decline participation.)
- The opportunity of informed consent was withheld from the victims of Thalidomide use. (Because clinical trials for Thalidomide were incomplete, the women who used the drug became, in effect, research subjects for its effects on pregnant women. These “subjects” were not informed that the risks were unknown, and so were unable to make an informed decision of whether to participate.)
- The opportunity for continued informed consent was withheld from the Tuskegee Study subjects. (Subjects were not fully informed of their diagnosis, nor were they given the opportunity to withdraw from the study once treatment became available.)

In addition to informed consent, respect for persons includes the protection of those with diminished autonomy. 45 CFR 46 Subparts B-D are an outgrowth of the principle of respect for persons, and discuss the protection of persons who may not have the ability to fully weigh their choices, or do not feel that they have a choice at all. For research involving children or others with diminished capacities, informed consent must be given by a legally authorized representative (LAR) and informed assent must be given by the subjects. For research involving prisoners, the investigator must pay special attention to the ability of the subjects to make a truly voluntary and uncoerced decision to participate.

**Beneficence**

The principle of beneficence is concerned with weighing the potential for harm to the subjects participating in the research against the benefits the research may produce, or the conducting of a risk-benefit analysis of the proposed research. In many ways, beneficence is the most difficult of the three principals to operationalize.
The *Belmont Report* refers to the Hippocratic oath, which requires physicians to “benefit their patients according to their best judgment.” However, when the potential for benefits apply not to the subjects themselves, but to future or simply other populations, it becomes even more difficult to weigh the potential for these future benefits against the potential for current and/or ongoing risk to the research subjects. The *Belmont Report* further acknowledges one’s “obligation to recognize” and take into account the longer-term benefits of the research, such as the potential for its overall contribution to science.

**Justice**

The concept of equality in the distribution of burdens and benefits forms the backdrop of the *Belmont Report*’s discussion of the principle of justice. In addition, the report references the research performed in the Nazi concentration camps and the Tuskegee syphilis study as examples of particularly flagrant injustice. In the realm of research, justice is concerned with ensuring the potential benefits of the research apply to the population from which the subjects were recruited, and the potential harms be distributed fairly. In other words, subjects should not be recruited simply because they are easily available (a “convenient” population), but be a random sampling of subjects representative of the population which stands to benefit from the research.

**The Federalwide Assurance**

The IRB is overseen by the Office of Human Research Protections (OHRP), under the Department of Health and Human Services (HHS). All Federally funded human subjects research must be conducted under a Federalwide Assurance, or contract entered into by OHRP and the institution with oversight for the research. This contract stipulates that all federally funded research conducted under the auspices of that institution will comply with the federal regulations. Brandeis University operates under Federalwide Assurance #FWA00004408.

While the regulations apply only to federally funded research, Brandeis University believes the protection of human subjects in research is vital and has determined that all research conducted under the auspices of the university or by any member of the Brandeis community will be reviewed by the Brandeis University IRB and held to the same standards, whether federally funded or not.

**IRB Membership**

The federal regulations stipulate that each IRB must have at least five members with varying backgrounds including, at a minimum:

- **One member who has formal education and training in scientific areas relevant to the research it reviews.** For example, an IRB that reviews primarily social scientific research must include a minimum of one social scientist, whereas an IRB that reviews primarily biomedical research must include at a minimum one member with a biomedical background.

- **One member whose formal education and training are in non-scientific areas,** who can provide input from a non-scientific vantage point.

- **One member who is not otherwise affiliated with the institution in any way,** who is sensitive to and can represent community attitudes. If possible, this member should be representative of the population from which the research draws its subjects.

In addition, the committee members must be diverse, taking into consideration race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes; must be knowledgeable in institutional regulations, applicable law, and standards of professional conduct and practice; and, if the IRB regularly reviews research with a specific vulnerable population, include a member who is knowledgeable about and experienced in working with this population. Note that, with regards to research involving prisoners as subjects, one member of the board must be a prisoner or prisoner representative with the experience to serve as a representative of the prison population.
The Brandeis University IRB is a diverse group and includes members of the faculty, administration, and community with scientific knowledge, an understanding of community mores, and specific knowledge about regulations and the protection of human subjects research.

**IRB Responsibilities**
The overriding responsibility of the IRB is to safeguard the rights and welfare of human subjects in research. In so doing, the IRB ensures its members:

- Have the accumulated professional competency necessary to review all proposals
- Participate in mandatory and ongoing training
- Understand the Federal regulations and institutional policies related to human subjects research
- Attend monthly IRB meetings and actively participate in discussions, offering their unique point of view
- Avoid conflicts of interest
- Maintain the confidentiality of the meetings
- Review each proposal according to the Federal regulations

**Criteria for Approval**
To fulfill its responsibility for the protection of human research subjects, the IRB, guided by the federal regulations, reviews each proposal by the following criteria:

- *Risks to subjects are minimized.* Every research project incurs some risk (examples include, but are not limited to, psychological, social, economic, legal); however, these risks must be warranted and a discussion of all risks must support their necessity.

- *Risks to subjects are reasonable in relation to anticipated benefits.* A risk-benefit analysis is conducted to ensure the potential for harm is warranted based on the possibility and probability of the benefits. Benefits to be considered are those that may be gained directly from the research; possible benefits for the future (e.g., possible effects of the research on public policy) are not considered.

- *Selection of subjects is equitable.* Such things as the inclusion/exclusion criteria; appropriateness of potential subjects; distribution of potential benefits; recruitment methods; and possibility for coercion, including compensation offered, are considered.

- *Informed consent will be sought from each prospective subject.* Or, in those instances when the subject is a child or cognitively impaired, the subject's assent and consent from the subject's LAR.

- *Informed consent will be appropriately documented,* and requests for waivers appropriate to the situation.

- *Research plan makes adequate provision for monitoring the research data,* and is appropriate for the risk level of the project. Consideration will be given to where it will be stored, how it will be stored, and for how long it will be stored. Note that Brandeis University strongly encourages investigators to use box.com for data storage whenever possible.

- *Adequate provisions are made to protect the privacy of subjects,* such as for methods of recruitment and data collection.
• *Adequate provisions are made to protect and maintain the confidentiality of the data*, such as use of codes linking identifying information to data, separation of face sheets from data, and limiting accessibility to data to protect subjects’ confidentiality.

• *Additional safeguards are included for subjects vulnerable to coercion or undue influence*, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

**Levels of Review**

There are three levels of review for IRB protocols:

**Exempt:** Projects that meet the requirements for one or more of the exempt status categories specified in the federal regulations; involve no more than minimal risk to subjects; do not place subjects at risk for criminal or civil liability, or damage their financial standing, employability, or reputation; do not involve deception (incomplete disclosure may be allowed if subject agrees to the incomplete disclosure prospectively); do not involve children unless expressly allowed by the category of review; and do not involve prisoners (or their data), undergo review by a qualified HRPP staff member and/or by an IRB member designated by the Chair.

**Expedited:** Projects that meet the requirements for one or more of the expedited categories specified in the federal regulations; involve no more than minimal risk to subjects; and do not involve prisoners (or their data), undergo review by one or more IRB members designated by the Chair.

**Full Committee:** Projects that do not meet the requirements for exempt status or expedited review and/or are greater than minimal risk undergo review by the full IRB committee at a convened meeting in which there is a quorum of members.

**Minimal Risk**

A research study is considered minimal risk if the probability and magnitude of harm or discomfort anticipated in the proposed research is not greater, in and of itself, than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**IRB Review Authority**

The federalwide assurance under which Brandeis University's IRB operates gives the IRB the responsibility and authority to make the following determinations as a result of its review of proposed research based on the above criteria: 1) approve the proposed research, 2) require modifications and re-review the revised proposal, or 3) disapprove the proposed research. (Note that a proposal can only be disapproved after review by the full committee – if an exempt or expedited status reviewer feels the research should be disapproved, or if s/he feels that the research does not fall into an exempt or expedited category, they may refer the proposal to the full committee for review.) Once the determination is made, the IRB has the responsibility to notify the investigators of its decision in writing. For those proposals the IRB disapproves, an explanation is included with the notification and the investigator is given the chance to respond.

In addition to its initial review, and as a consequence of its appraisal of the degree of risk to subjects in the proposed research, the IRB develops a timeline for the continuing review of all non-exempt/expedited research, which it has the responsibility of conducting at a minimum of once per year.

Note that, while it is the responsibility of the IRB to review the proposed and ongoing research, it is the responsibility of the investigator to accurately report to the IRB its planned and conducted research during the review processes. This includes submitting to the IRB for its review and approval requests to modify its approved research plan. Should the IRB become aware of research being conducted without, or not in accordance with, its approval, it has the responsibility and authority to suspend or terminate the research through the withdrawal of its approval. This authority to suspend or terminate research extends, as well, to research which is thought to have resulted in unexpected serious harm to its subjects.
References
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http://www.cdc.gov/tuskegee/index.html

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http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

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