

STANDARDS CASE STUDY: INSTITUTIONAL REVIEW BOARDS

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1 Introduction

All research with human subjects in the United States must be approved by an institutional review board (IRB) if it receives any funding from the US government or if it will be used to get something approved by the FDA. Rather than directly enforce regulation on medical research itself, the federal government mandates that local boards enforce its regulation on medical research.

This seems like one of the most high impact and widely enforced standards in the US. Cost estimates for the IRB system indicate that society probably annually spends over a billion dollars and forgoes at least thousands of lives potentially saved in order to follow the principles of medical research ethics - which likely reduces the number of deaths due to medical research by between zero and two orders of magnitude.¹

Here are my favorite sources I found while writing this case study:

- *A Systematic Review of the Empirical Literature Evaluating IRBs: What We Know and What We Still Need to Learn* by Lura Abbott and Christine Grady. [1]
- *Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform* by George Silberman and Katherine L Kahn. [2]
- *Book Review: From Oversight to Overkill* by Scott Alexander. [3]
- *Protections for Human Subjects in Research: Old Models, New Needs?* by Laura Stark. [4]
- The AMA Journal of Ethics's April 2009 Issue titled *Ethics in Clinical Research*. [5]

2 Current Process

2.1 How It Works (Briefly)

Before beginning any research involving human subjects, the researchers must first get approval from an IRB. The researchers submit an application for their research which describes their study and the potential risks involved. The IRB has “the authority to review and approve, require modifications in, or disapprove all research involving human subjects.” [6] The IRB also has the “authority to conduct continuing review” of the research to ensure that its recommendations are followed and that there is no unexpected serious harm. [6] Demonstrating compliance requires detailed records to be kept throughout the study.

Each IRB is a separate organization, run by a medical research institution or private company, rather than having all IRBs be part of a single regulatory agency. There is significant variability in how each IRB is run, and some are more or less restrictive and more or less efficient than others. [1] They are required by the Office for Human Research Protections (OHRP) to enforce federal regulations on research with human subjects, known as the Common Rule. [7]

2.2 Relevant Law

Institutional Review Boards were created by the National Research Act of 1974:

The Secretary shall by regulation require that each entity which applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an 'Institutional Review Board') to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research. [8]

This act also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to establish the principles that IRBs would operate under. Over the next several years,

¹See Appendix A for these estimates.

the commission wrote reports and recommendations for multiple areas of research.² The most general (and most readable) of these is the Belmont Report of 1978.[10]

The Belmont Report begins by establishing the boundary between medical practice, “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success,” and medical research, “an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.” It then describes three basic ethical principles for research involving human subjects: respect for persons, beneficence, and justice. “Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.” Beneficence involves two general rules: “(1) do not harm and (2) maximize possible benefits and minimize possible harms.” Justice involves “the sense of ‘fairness in distribution’ or ‘what is deserved.’ An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.” Consideration should be given to “who ought to receive the benefits of research and bear its burdens?” The Belmont Report closes by looking at applications of these general principles to informed consent, risk/benefit assessment, and the selection of subjects of research.

These reports were incorporated into the Code of Federal Regulations Title 45 Part 46 in 1981. They have been revised several times since then, including in 1991, 2009, and 2018. The 1991 version was adopted by more than a dozen federal agencies in addition to the NIH, and since then, 45 CFR 46 has been known as the Common Rule.[7] The Common Rule includes some of the technical details about what is and is not acceptable, for example, there are about 3,000 words about what is required for informed consent in various scenarios. Further details of the regulation are also created by individual IRBs, and vary between different IRBs.

2.3 Local vs Independent IRBs

There are two types of IRBs: local IRBs and independent (or central) IRBs.³

Local IRBs are created and run by a particular institution, often a hospital or university, which performs a significant amount of research with human subjects. All research involving human subjects conducted at that institution must be approved by the local IRB before the study can begin.

Independent IRBs are not associated with any particular institution doing research with human subjects. They are typically for-profit companies, which make money by having researchers pay the IRB to review their proposed research. Independent IRBs seem to be less restrictive than local IRBs: researchers can ‘shop around’ for an independent IRB which seems likely to accept their work, although they are required to inform the IRB about any previous decisions.

This case study focuses on local IRBs because most research with human subjects occurs at institutions with a local IRB.

2.4 Who Is on an IRB?

An IRB must “consist of at least five men and women of diverse backgrounds and sufficient maturity, experience and competence.”[6] At least one member must not be affiliated with the institution conducting

²Wikipedia lists the following:[9]

- Research on the Fetus (1975)
- Research Involving Prisoners (1976)
- Research Involving Children (1977)
- Psychosurgery Report and Recommendations (March 1977)
- Disclosure of Research Information Under the Freedom of Information Act (April 1977)
- Research Involving Those Institutionalized as Mentally Infirm (1978)
- Ethical Guidelines for the Delivery of Health Services by DHEW (1978)
- Appendix to Ethical Guidelines for the Delivery of Health Services by DHEW (1978)
- Institutional Review Boards (1978)
- Special Study Implications of Advances in Biomedical and Behavioral Research (1978)
- The Belmont Report: Ethical Principles and Guidelines for Protection of Human Subjects of Biomedical and Behavioral Research (1979)

³A good summary of the distinction was given by Moon in the 2009 special issue of the AMA Journal of Ethics.[11]

the research; this is often a religious or other community leader. IRBs are encouraged to be representative in terms of gender, race, and ethnicity, although this is not strictly required.

IRBs also have advisors who are experts in medical ethics and medical law. The advisors' job is to ensure that the decisions of the IRB are consistent with the relevant law and regulations. It seems as though these advisors often have at least as much influence on the IRB's decisions as the members of the IRB itself. Staff salary seems to account for the majority of the cost of running an IRB, and the amount spent on the salaries of the board itself is typically much lower.⁴

2.5 How Are Regulations Enforced?

IRBs operate under an approval model of regulation.

Research involving human subjects must first get approved before the study can begin. This process seems to almost always involve the IRB making recommendations, which the researchers have to implement or abandon the study. The researchers can try to convince the IRB to retract one of their recommendations, but there does not seem to be any appeal process if the IRB refuses. As long as the study is ongoing, the IRB re-reviews the research at least annually.

The Office for Human Research Protections (OHRP) in the U.S. Department of Health and Human Services has oversight over IRBs. OHRP has the power to audit any ongoing study that requires IRB approval. Audits seem to mostly involve checking the documentation for the study, rather than sending auditors to directly observe the research. Auditors have the power to shut down any study found to be in violation of the regulations, or to recommend further changes to the study. These audits do seem to be intensive and often require modifications. If an institution's IRB is found to be systematically violating regulation, OHRP can shut down all ongoing studies at that institution. This is rarely done, but the threat seems to encourage local IRBs to be very cautious.

Independent IRBs are also audited, although they seem to be more difficult to get to consistently enforce regulation. An additional enforcement mechanism involves 'sting' operations. The Government Accountability Office can create a fake IRB application for an experiment that should be rejected under the Common Law and submit it to several independent IRBs. Any IRBs which approve the application can then be required to submit to further audits, change their policies, or be shut down.^[14]

The National Research Act only explicitly applies to federally funded research. Whether something is federally funded is determined at the institution level, not at the study level: studies which do not receive federal funding themselves must still get IRB approval if they are conducted at a hospital which receives federal funding. Because of how thoroughly intertwined the federal government and health care spending are, this includes almost all institutions which might do medical research with human subjects.

Some kinds of studies involving human subjects do not require IRB approval, for example, marketing and customer satisfaction studies. These are not considered "research" because their goal is not "generalizable knowledge," which is part of the Belmont Report's definition of research. Universities can do marketing research and teacher evaluations for themselves without IRB approval, unless they intend on publishing those results as general characteristics of the market or general evidence about teaching.^[15, 16] This feels like an important loophole for the social sciences, although it is not as important for medical research because doctors are required to maintain the standard of care for patients not involved in medical research.⁵

⁴Speckman et al. estimate that staff salaries account for 59% of the cost of running an IRB and board salaries account for 28% of the cost.^[12] Byrne et al. estimate that staff salaries account for 65% of the cost of running an IRB and board salaries account for 22% of the cost, and that the staff : board cost ratio varies wildly, from 0.33 to 11.30.^[13] I think that these are the same survey, with different ways of analyzing the data.

⁵California law defines 'the standard of care' as:

[A/An] [insert type of medical practitioner] is negligent if [he/she/nonbinary pronoun] fails to use the level of skill, knowledge, and care in diagnosis and treatment that other reasonably careful [insert type of medical practitioners] would use in the same or similar circumstances. This level of skill, knowledge, and care is sometimes referred to as 'the standard of care.'^[17]

There are also some indirect enforcement mechanisms. If a study which tests a new product does not have the required IRB approval, the FDA will not accept that study as evidence for the safety or efficacy of the product.[18] Most prominent medical journals require something similar to IRB approval: they require “registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.”[19] These downstream enforcement mechanisms remove some incentives researchers might otherwise have to avoid IRB approval.

My impression is that most medical researchers agree with the basic principles of medical ethics, but find IRBs to be too restrictive or arbitrary in practice.⁶ It seems as though these regulations are more imposed on medical researchers than followed because medical researchers endorse them.

The regulations which IRBs are meant to uphold do seem to be consistently enforced across almost all medical research.

3 History

3.1 Pre-IRB Failures

IRBs were created in response to unethical medical experiments. They did not ‘get out in front of’ the risk.

International principles for medical ethics were established in response to experiments performed by Nazi doctors during the Holocaust. The Nazi Doctors’ Trial after the war resulted in the creation of the Nuremberg Code and the Declaration of Helsinki by the World Medical Association.[21, 22]

The particulars of American medical ethics, including our system of IRBs, were developed in response to unethical medical experiments conducted in the U.S. which became publicly known in the 1960s and 70s. The most influential of these were:⁷

- **Tuskegee Syphilis Study.** The Public Health Service recruited hundreds of impoverished African American men with syphilis to study the progression of the disease, and did not treat them even after penicillin was invented and became the standard treatment of syphilis.
- **Hepatitis Studies at Willowbrook State School.** Mentally retarded children were fed live hepatitis virus to better understand the disease’s transmission at the school.
- **Jewish Chronic Disease Hospital Study.** Live human cancer cells were injected into elderly patients without cancer to monitor if and how their body rejected them.

The main mechanism of change here seems to be: (1) unethical research with human subjects takes place, (2) medical researchers who are aware of the project publish or ask journalists to publish descriptions of these experiments, (3) the public and media react with outrage, (4) public outrage pressures decision makers in Congress or federal agencies to do something, and (5) Congress or federal agencies change the relevant policies to try to prevent something similar happening in the future. For example, for the Tuskegee Syphilis Study, an epidemiologist at the US Public Health Service, Peter Buxtun, told a reporter at the Associated Press, Jean Heller, who published the story, and the 40 year long study was halted four months after the story was published.[24]

IRBs were designed to prevent these sorts of things from happening, and they have been successful at this. These sorts of egregious violations of medical research ethics do not seem to have happened in the US since the 1970s.

⁶The best evidence for this I’ve found is a survey by Whitney et al.[20] They point out that their sample size is too small (28 respondents) to draw quantitative conclusions from, and that there are both positive and negative views of IRBs represented. There are more negative comments, and the negative comments seem much more negative than the positive comments are positive.

⁷These were the most famous, but not the only examples. Beecher published a list of 22 unethical or questionably ethical studies in 1966.[23]

3.2 Precursors

There were some precursors to IRBs. These seem mostly to consist of local actions by the federal government, rather than the development of private standards.

The National Institutes for Health (NIH) created the first human subjects review board, the Clinical Research Committee (CRC), at their research hospital, the Clinical Center, in Bethesda, Maryland in 1953. The creation of this committee seems to have been dual purpose: the goal was both to protect patients and to protect the Clinical Center from public and legal criticism while researchers performed bolder research than doctors typically did.[4]

The most significant related private standards seem to be the AMA Code of Ethics, initially adopted in 1847 and revised many times since then.[25] These are ethical standards for medical practice, not medical research, and so they seem only tangentially related to the development of IRBs.

3.3 Spread and Legislation

During the 1960s and 70s, public outcry in response to unethical medical experiments led to increased regulation by federal agencies and Congress, and to the creation of IRBs.⁸

In 1964, the public learned about the Jewish Chronic Disease Hospital Study - and that it had been partly funded by the NIH. The NIH avoided legal responsibility by arguing that their ethics procedures only applied at the Clinical Center. There was increasing pressure from Congress to have the CRC review all research funded by the NIH. James Shannon, then head of the NIH, instead directed institutions and researchers receiving NIH funding to be approved by their own local committee of experts. This led to a proliferation of CRC-like human subjects review boards.

In 1972, the public learned about the Tuskegee and Willowbrook studies. It seems like the public, professional organizations, and legislators were getting increasingly upset by the state of medical ethics in the country. In 1969, the American Academy of Arts and Sciences had published a special issue of *Daedalus* on medical ethics.⁹[26] Congress responded to these pressures by passing the National Research Act of 1974, described above, which mandated the creation of IRBs. This act also created a commission which wrote reports governing more detailed policies for IRBs, including the Belmont Report.

3.4 More Recent Developments

In 2001,¹⁰ a patient taking part in asthma research at Johns Hopkins died. The experiment does not seem to have been nearly as unethical as the studies before 1974, but the public and Congress were outraged. Gary Ellis, head of the Office for Protection from Research Risks (OPRR, which later became OHRP), responded by shutting down almost every medical study at Johns Hopkins and a dozen other research institutions.

Institutions conducting research with human subjects seem to have responded by becoming much more cautious about the legal risks of research involving human subjects. The number of advisors to IRBs dramatically increased,¹¹ and it seems as though the relative power of the IRBs themselves and their advisors shifted decisively towards the advisors.

The system of IRBs has remained largely the same from then until today.

4 Further Research

Several questions about IRBs might be interesting to address in more detail:

⁸My telling of the history follows / combines the histories told by Scott Alexander and Laura Stark.[3, 4]

⁹Alexander's telling of the history describes this issue of *Daedalus* but not the Belmont Report. Stark's telling of the history describes the Belmont Report, but not this issue of *Daedalus*. Both happened. I am inclined to agree more with Stark that the Belmont Report is more important since it is a legally binding document.

¹⁰Alexander's telling of the history puts this in 1998, but other sources say that it occurred in 2001.[27, 28, 29]

¹¹"The staff of the Northwestern IRB, for instance, grew between the late 1990s and 2007 from two people to forty-five." [3] This is presented by Alexander & Whitney as being typical.

- The weakest spots in the regulations seem to involve independent IRBs. How different are independent IRBs from local IRBs and how does the federal government enforce its regulations on them? This case study looks at this question a little, but it could be investigated further. Something like independent IRBs has been proposed as a model of AI governance.[30]
- Most of the discussion about how IRBs function focuses on IRBs at universities and major hospitals. There are also large private companies that focus on medical research. How are local IRBs at e.g. pharmaceutical companies different from local IRBs at universities?
- Some of the enforcement for IRBs comes from the FDA. How do IRBs and the FDA interact? It seems like the result is multiple layers of defense for medical ethics.
- How did the particular regulations that make up the Common Rule come to be included?
- How do the medical ethics systems in other countries work? Do they use IRBs, direct regulation by a government agency, or some other system? See Appendix B for a preliminary investigation into this.

5 Conclusion

Institutional review boards are highly effective at enforcing their understanding of medical ethics on almost all research involving human subjects in the United States, even though the cost to medical researchers is substantial. There are a few loopholes involving overly permissive independent IRBs or research done entirely independently of federal health care spending. These loopholes are not available to most medical researchers because most research with human subjects is done at institutions which have local IRBs.

IRBs function using an approval model of regulation. Research involving human subjects must be approved before it can begin. There are audits of the research by the IRB, and of the research and IRB by OHRP. These audits require and rely on extensive documentation. Any study found to be not in compliance can be shut down.

The development of IRBs occurred largely in response to, not ahead of, unethical medical experiments. Public outrage at these experiments drove federal agencies and Congress to act.

A Estimating Costs and Benefits of IRBs

A.1 Estimates of Costs of Complying with Medical Ethics

To understand the impact of IRBs, and so how much our society is willing to pay in order to follow medical ethics, we should try to estimate the cost of IRBs. There are three things that could be estimated here: the operational cost of running the IRB to the institution conducting research with human subjects, the cost to medical researchers in order to comply with IRBs, and the cost to society as a result of having slower medical research than we would if we were concerned with medical ethics.

Scott Alexander estimates the operational costs to be about \$100M per year, the compliance costs to be about \$1.5B per year, and the societal cost to be maybe 10k - 100k preventable deaths of Americans per year.[3] I think the source for these numbers is Whitney's book, but this is not explicitly said.

A survey of 123 medical schools (69 responded) in 2002 provides the best estimates I have found of the operational costs of IRBs. It found that the median annual cost per institution is about \$800k.[12] Multiplying this by the number of medical schools is about \$100M per year. There are currently 2,300 IRBs in the US in total, at 1,800 institutions.[31] If we were to assume that medical schools are typical, this would imply about \$1.5B in operating costs. Medical schools probably do more research, and more complicated research, than the median institution with an IRB, so this is probably an overestimate. The survey also estimates a median of \$560 per review, with significant economies of scale.[13] There were about 270k applications per year in 2008,[32] which would imply a cost of about \$150M per year. If medical schools are larger than most

institutions and there are economies of scale, then this is likely an underestimate. My order of magnitude estimate of the annual operational costs of IRBs is $\$10^8 - 10^9$.

Estimates of the cost to researchers are harder to find. One review article asked the question, but demurred to answer it because the data is not available.[2] Some individual multisite studies spend \$50k - 100k to comply with every local IRB, although these studies are not representative.[2] My impression is that the costs for medical researchers to comply with IRBs is significantly larger than the costs of running the IRB itself. An estimate of the total monetary cost to the medical research system should be at least twice the operational costs of the IRBs themselves.

Estimates of the societal costs of IRBs as a result of slow medical research are even harder. Individual instances of slowed medical research seem bad. My order of magnitude estimate of not doing human challenge trials for COVID-19 vaccines is about 100,000 lives lost in the US.[33] The IRB delay in ISIS-2, which investigated using a combination of streptokinase and aspirin when treating heart attacks, resulted in 6,000 additional deaths.[3] I don't know how to extrapolate from individual instances to the total cost: it is plausible that the majority of the total cost comes from a few of the worst instances. I am going to say that the average annual cost to society of IRBs slowing medical research over their 50 year history is at least thousands of lives potentially saved.

These cost estimates are large enough that I think that it is reasonable to say that our society has shown that it is willing to pay significant costs in order to follow the principles of medical research ethics.

A.2 Estimates of Deaths Due to Medical Research

To understand the benefits that enforcing the principles of medical ethics has had, we should look at how much harm has been caused by medical research before and after the introduction of IRBs.

I expect that most of the harm caused by medical research has occurred in a few of the worst instances. The Tuskegee Syphilis Study resulted in more than 100 men dying from syphilis or complications related to syphilis over 40 years.¹² This is a rate of about 3 deaths per year. These deaths could have definitely been prevented, at least after the adoption of penicillin as the standard treatment for syphilis in 1947. The Hepatitis Studies at Willowbrook and the Jewish Chronic Disease Hospital Study both involved fewer people, and I have not seen claims that people died as a result of participating in the study. There could also be other studies which caused people's deaths that I do not know about. I think that single digits of preventable deaths per year is a reasonable order of magnitude estimate for the cost of not having a system enforcing research ethics in 1970.

There is significantly more medical research now than in 1970. Total research funding from the federal government has increased by a factor of 3 since 1970, and the share of funding going to the life sciences has risen from 29% to 48%.[36] If harm due to medical research scaled with federal life science funding, we would expect that there would be 15 preventable deaths per year. This is a very rough estimate. Federal funding to the life sciences is an imperfect proxy for the number of people enrolled in clinical trials: not all medical research is funded by the federal government and the amount of funding per person enrolled could have changed. I think that double digits is a reasonable order of magnitude estimate for the number of preventable deaths per year that we would have if IRBs were not created in the 1970s.

The number of preventable deaths in medical research today is also disputed. People who think that IRBs should become less strict claim that there have been 5 instances of unexpected deaths from research in the last 25 years.[3] This corresponds to 0.2 deaths per year. People who think that IRBs should become more strict claim that there have been 153 instances of treatment-related deaths in clinical trials over four years.[37] This corresponds to 38 deaths due to medical research per year. The difference between these two estimates is probably due to how "unexpected deaths from research" and "treatment-related deaths in

¹²Wikipedia claims that 28 men died directly from syphilis and 100 men died from complications due to syphilis, although I have not tracked down their source.[34] Several other websites seem to be quoting Wikipedia. The New York Times reporting in 1972 estimated that the number is 107. By then, 357 people involved in the study had died, but it was not clear how many had died due to syphilis. Only 92 of the men who had died had had autopsies performed, and of these, 28 had died due to syphilis (30.4%). If we assume that this selection was representative, and syphilis was the cause of death in 30% of the 357 men who died, then the estimate is 107.[35]

clinical trials” are operationalized. I am not sure which is more valid, so I will say that IRBs have reduced the death rate due to medical research by zero to two orders of magnitude.¹³

B Medical Research Ethics in Other Countries

Understanding how medical research ethics works in other countries can help give perspective for how the IRB system in the United States works and was developed. This is a larger subject than understanding how IRBs work in the US, and I have spent less time investigating it, so I am not as confident in this appendix.

Nevertheless, here are some potential takeaways:

- Things are complicated and different countries use very different systems.
- Society is structured differently in different countries, and this affects how the medical ethics system works.
- Even weak international pressure can transmit principles.

The principles of medical research ethics are surprisingly similar between different countries, probably because of international influence, while the systems to enforce medical research ethics are quite different, probably because the society is structured differently.

B.1 Things are Complicated

Different countries have a wide variety of ways of enforcing medical research ethics.

One way to observe this is to attempt to do a medical study across multiple European countries. Several groups that have done this have written pages describing their experiences complying with all of the medical ethics systems, which can be called IRBs, research ethics committees, or something else.

One study described the possible systems as:[38]

- Primary central IRB review,¹⁴ then start research in the entire country after approval (Denmark, Finland, France, Norway, Sweden).
- Primary central IRB review, then start research in the affiliated center after approval and additional extensive IRB approval in other centers (Belgium, Germany, Hungary, Italy).
- Primary central IRB review, then start research in the affiliated center after approval and additional marginal IRB approval in other centers for feasibility (Netherlands)
- Primary central IRB review not affiliated with a particular center, then additional marginal IRB approval in other centers for feasibility (United Kingdom).
- Primary local IRB review for every center (Austria, Latvia, Romania, Serbia, Spain, Switzerland).
- Primary local IRB review, but one center’s approval allows research to begin in the entire country (Lithuania).

Some of the review processes seemed dramatically more stringent than others: the IRBs in Romania and Serbia approved this traumatic brain injury study in one day, while some other IRBs took more than a year to get through the review process.

A different study classified countries as having a national/regional ethics committee (Austria, Belgium, Estonia, France, Hungary, Israel, Poland, UK), local ethics committees (Croatia, Germany, Greece, Ireland, Italy, Netherlands, Serbia), or both (Czech Republic, Portugal, Spain).[39] Not only are these different categories, for some countries the description is very different. I do not know why that is.

¹³I find it weird that people who argue that IRBs should be stricter use data indicating that IRBs have had little effect, while people who argue that IRBs should be less strict use data indicating that IRBs have had a significant effect. I guess that the argument over how important a problem this is determines the bias, rather than the argument over whether IRBs have been effective.

¹⁴“Primary” here means the first or only review board you have to apply for. “Central” here means that the review board has jurisdiction over the entire country. For this system, you only need to get approval from the one central review board, and then you can begin research anywhere in the country.

B.2 Societies Are Structured Differently

The medical industry includes professional associations of doctors, hospitals (which may be public or private), government agencies, and various private companies (pharmaceuticals, insurance, etc.). The legal system includes legislation, case law, and regulations written by government agencies. The ethics community consists of philosophers, theologians, and activists. Medical research ethics sits at the intersection of these and so could involve any or all of these stakeholders.

The relative power of and relationships between these stakeholders is different in different countries. The Anglosphere’s tradition of legal precedence works differently from France’s stronger focus on legislation. Philosophers in the US who endorsed American pragmatism got involved in medical ethics more quickly than their more abstract British counterparts, while the closer institutional relationships between the church and state in the UK allowed theologians more influence there.¹⁵[40] The development of medical research ethics involved a negotiation between these various actors. The different structures of society caused these negotiations to play out in different ways.

Western countries typically have centuries-old doctors’ associations, like the American Medical Association in the US, the Royal College of Physicians in the UK, or the Academy of Medicine in France. In 1950, all of these organizations were self-regulating. A common pattern in the development of medical research ethics is the transfer of regulatory power from the doctors’ associations to the government or other parts of society. How this happened and who ended up with the regulatory power varied widely between countries.

B.3 Even Weak International Pressure Can Transmit Ethical Principles

The United States was the first country to develop medical research ethics, and has had little influence from other countries. Even international codes that predate the American system, like the Nuremberg Code, were often written by Americans.

International influence has been more important for other countries, even without significant intergovernmental pressure. In some countries, international influence was the impetus for starting a national discussion around medical ethics, some countries apply international regulations as law, and some countries wholesale adopted another country’s system of medical research ethics.

The first ethics committees in the UK were created to comply with the (American) NIH.[41] Some British hospitals wanted to collaborate with American researchers in the late 1960s, but the NIH refused to provide funding for this collaboration unless they got approval from a local IRB. Several British hospitals created American-style IRB. This provided part of the impetus for discussions between the Royal College of Physicians, the NHS, hospitals, advocacy groups like the Patients Association, and Parliament that would create the British system of medical ethics and enforce it on all medical research institutions.

In France, international influence was more likely to come through the World Medical Association and the European Union than directly from the United States.[42] The Nuremberg Code, the Helsinki Declaration, and subsequent declarations would be incorporated into EU law, and EU law is binding in France. National legislation passed by the French Parliament is also important, but EU law keeps anything from being too different from other countries. One difference that does exist is that France does not require surveys to undergo ethical review. However, some American journals require IRB approval to publish survey results, so there are a few American-style IRBs in France for surveys intended to be published in the US.

International influence has been even more important in some non-Western countries. In Singapore, medical research ethics developed in the late 1990s, when the government decided that their “will to modernize” should include developing a medical research industry.[43] Part of the “soft infrastructure” for this goal was a system of medical ethics that established and maintained Singapore’s reputation among Western researchers and multinational corporations. Singapore adopted the British system of medical ethics, with little negotiation with organizations or people within Singapore.

¹⁵My impression is that churches in the US get more involved in the political process, while the Church of England has a closer relationship to various government agencies.

China did not copy a Western model as explicitly as Singapore, but it still was heavily influenced by Western practice.[44] China's first IRBs were created in the 1980s, at a few medical institutions that wanted to take part in joint international research. The resulting system ended up being similar to the American one: in 2007, the Ministry of Health issued regulation mandating that any hospital doing research with human bodies have an IRB to approve and regularly review that research. One important difference from the American system is that most research hospitals in China are public, while in the US many research centers and their IRBs are private. I am skeptical of the effectiveness of the Chinese IRB system in providing systematic or universal protection because there are credible reports of China using unethical medical procedures and research as a tool of oppression against religious minority groups.[45] Still, it is striking that China uses a western system to protect the people it wants to protect from abuses in medical research.

The basic principles of medical ethics seem to be very widely accepted. The Belmont Report in the US lists the basic ethical principles as respect for persons, beneficence, and justice, and their main applications as informed consent, risk/benefit assessment, and the selection of subjects of research.[10] China's four main aspects of ethical norms are informed consent, acceptable risk-benefit ratio, privacy protection, and justice.[44] In addition, "French researchers have adopted these rules of Anglo-Saxon origin." [42] The international influence needed to get these principles adopted was sometimes very weak, consisting only of the desire to collaborate with American researchers and publish in American journals.

In contrast with the widely spread principles of medical research, the systems in place to enforce them are often very different. While international influence often gets the first American-like IRBs started, what ends up being created is the result of negotiations between various stakeholders. Since different stakeholders have different relevant power and relationships in different countries, the resulting institutions designed to enforce medical research ethics are often very different.

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