The Recipe for Over-Reaching Regulation

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Recently, I was at a meeting with more than 20 individuals from various disciplinary backgrounds. In the midst of our planned discussion of the ethical, legal, and social issues surrounding research into the human microbiome, an IRB meeting broke out. By that, I mean that the agenda included no planned discussion of how federal regulations would apply to a particular informed consent form. And yet, when confronted with such a consent form, its content dominated nearly an hour of discussion without any satisfactory consensus or resolution. As a member of biomedical science and social science IRBs for several years, this did not surprise me.

I share sympathies with the arguments for research exceptionalism as offered by Wilson and Hunter (2010), and do not address, in a substantive way, any of their points in this commentary. Instead, I identify three features of the federal regulations and their application that produce Institutional Review Boards (IRBs) tendency toward over-reaching regulation.

First, the regulations are too broad. They attempt to cover all human subjects research with a single set of regulations; a difficult pose when crossing the lines between natural and social sciences research, and nearly impossible when crossing the lines from clinical trials to biobanks or humanities research. Second, the application of these regulations is uneven. The attempt to cover all research with a single set of regulations leads to ambiguous and vague language, which creates space for inconsistencies in interpretation across institutions and time. Third, the regulations foster a protectionist attitude. Failure to adhere to the federal regulations carries a substantial cost, and combined with the ambiguous language of these regulations, encourages tighter regulatory interpretations.

Parsing "Human Subjects Research"

Is it human subject research? This question is asked, either implicitly or explicitly, at the beginning of every review of an IRB application. Federal regulations provide definitions of each. The regulations define a human subject as, "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." (45CFR46.102) They also define research as, "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." (45CFR46.102) Together these definitions set up the parameters of federally funded research to which the regulations apply. In the remainder of this section, I delineate differences between activities that count as human subject research. These differences highlight the vast expanses between various inquiries that are expected to fall under a common rule.

Types of protocols that meet the established criteria for human subject research cross the expanse of the sciences. The regulations apply to a clinical trial to determine if a proven cancer treatment can also be used to treat macular degeneration. They also apply to an examination of the effects of living in a multi-lingual household on a child's speech

development. What these kinds of studies have in common is the careful analysis of rigorously gathered data. And yet, there is much that distinguishes them.

The former aims to find a treatment for a particular disease or condition and the latter aims to improve understanding of how home-life affects speech development. The former will study the aging and debilitated, the latter, the infantile and developing. The former will subject participants to the tangible physical risks of a medication known to produce iatrogenic harm, and the latter will subject them to the barely noticeable risks of observating parents and children at play.

Contrast both of these with yet another kind of research activity: establishing, maintaining and using a biobank. In the most common cases when biobank research requires IRB review, the risks associated with participant contributions are negligible—often, it is a blood draw or perhaps a biopsy taken as part of some other intervention. The spectrum of contributors to biobanks is also vaguely defined in many cases: it may be limited to individuals with specific conditions but also may not be limited at all—the contributors willingness and contingent presence are the only inclusion criteria. At the time of contribution, however, there are, at best, only vague aims or goals for the biobank.

Finally, compare all of these with those cases when oral histories require IRB review. That is, those cases when oral histories, normally exempt from these regulations, require review because the information gathered is linked to identifiable individuals and, "any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation." Take for example a historian interviewing former CIA agents about the use of torture. Here the risks of criminal and/or civil liability are palpable, but the similarities to other kinds of research ends there.

This first ingredient in the recipe for over-reaching regulation, the attempt to cover all human subject research with the same set of federal regulations, contributes directly to the production of the second ingredient: the ambiguity and vagueness of the language of the regulations and their subsequent uneven application.

Courting Ambiguity in Federal Regulations

IRBs are charged with a number of responsibilities when reviewing protocols, responsibilities that should be discharged following the language of the regulations that govern them. In this section I will use two examples ("generalizable knowledge" and "minimal risk") to illustrate that the language of these regulations is ambiguous and vague.

Take the use of the term "generalizable knowledge" in the definition of research. This term produces a large umbrella that appears to cover all the kinds of research enumerated in the previous section, and yet, in application the implications of the term are too broad. As an example, look to classroom exercises that are used to teach certain research methods or activities. It is generally accepted that these exercise do not meet the definition of research because they are not "designed to develop or contribute to generalizable knowledge."[1] And yet, there are two distinct and important ways that these activities may be designed to contribute to generalizable knowledge. First, intentions

[1] I do not have time here to provide any approaching a comprehensive list, but see for example: http://www.hrpp.umich.edu/classactivities.html

aside, there will be cases when the data gathered by students will produce results that advance the knowledge base for the subject-matter of the class. Second, the skills that the students are learning are meant to be applied to other areas and so there is very natural way in which these activities are meant to produce knowledge (for the student) that will be generalized (both in other areas and, perhaps, passed on to other students).

The motivation for exempting classroom exercises is easy to understand—it would be a substantial burden to instructors, students, and IRB members to review these exercises with unclear benefits. And yet, for all appearances it is a post hoc exception to the explicit language of the regulations.

A second example of the ambiguous or vague implications of regulatory language arises from the following definition of minimal risk: "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (45CFR46.102) If this regulatory language only applied to a single category of research (say, clinical trials), it could be more tightly defined, for example, to address the routine physical risks of harm or the ordinary social risks of breaching confidentiality. Because it must cover all categories of research, however, the language must remain abstract. This leaves open the possibility that "minimal risk" will mean widely divergent things for different trials. To put this in context, for the study of language development, minimal risk would seem to reference the risks associated with living in multi-lingual household while for the study of macular degeneration, the risks associated with diminishing vision, and so on. This vagueness is further complicated by the possibility of different participants in the same trial that are routinely subjected to different levels of risk. This might happen across trial arms (e.g., control versus experimental) or within trial arms (e.g., participants with differently expressed or more advanced versions of the same disease).

When IRB members are asked to determine whether a study meets the criteria for minimal risk, the language of the regulations provides only ambiguous guidance.

Institutionalized Protectionism

IRBs have explicit obligations that are aimed at protecting certain parties—specifically, research participants. These obligations regard both the adequacy of the informed consent form and the balance of risks and benefits.[2]

IRBs also have certain obligations that are not explicitly stated, but still arise from the nature of the federal regulations. If an IRB fails to adhere to federal regulations, the institution that they represent can have all federal monies suspended. A number of institutions have felt the weight of this failure over the last decade. This puts the IRB and its members in a position to protect the institution. That is, the application of federal guidelines that are explicitly designed to protect research participants are to be applied in such a way that the institution is protected from losing federal monies.

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[2] Balancing the risks and benefits of a study creates an interesting problem for IRBs that is, as yet, under-explored. On the one hand, determining whether the potential benefits are worth risks requires expertise in the area of research. On the other hand, IRBs are required to include many non-experts in the field who are still responsible to evaluate the risks and benefits. This topic is worthy of substantial treatment on its own and I will leave it aside for this short commentary.

The imagination of IRB members can be challenged by the attempt to imagine what a future participant will need to know and how to balance risks and benefits. In a similar way, their imaginations are challenged by the attempt to imagine how any auditor of IRB activities will interpret the ambiguous language of the federal regulations. Significantly, the risk is not that IRB members will interpret the regulations too strictly, that they will not allow research to proceed that they should have allowed. Instead, the risk is always that the IRB member will interpret the regulations too loosely, that they will allow something they should not have allowed. Such pressure incentivizes IRB members to interpret the ambiguous language of federal regulations as strictly as possible. Leading to what might be the most frustrating maxim of IRB activities: when in doubt, defer.