Published in final edited form as:

Am J Bioeth. 2017 July ; 17(7): 1–3. doi:10.1080/15265161.2017.1328899.

Modernizing Research Regulations Is Not Enough: It's Time to Think Outside the Regulatory Box

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We are a multi-disciplinary collaborative made up of bioethicists, social scientists, clinicians, and lawyers whose work focuses on the ethical challenges posed by a networked approach to biorepositories. Like many, we have been concerned that our human research regulations had become woefully out of date. While the interventional, hypothesis-driven research envisioned by the 1991 Common Rule remains important, contemporary research increasingly depends on the collection of samples and data for unspecified future research. Over the past decade, large collections of biological materials for research have grown in complexity and scope, creating inter-institutional, national, and international networks. These networks of biorepositories also are embedded in research pathways that leverage learning health systems, big data analytics, and sophisticated health informatics approaches.

While science has evolved in recent decades, it has had to do so within a regulatory framework best suited to individual, hypothesis-driven research studies. This approach is a poor fit for the research systems, collaborations, and multisite infrastructures that now are driving the future of precision medicine and translational science. We are interested in how networked biorepositories, which provide multisite infrastructure for research data and

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samples, have addressed human subjects protections challenges despite an ill-fitting regulatory framework.

For this reason, we followed with great interest the effort to update the Common Rule. During this six-year odyssey, we and other members of our professional communities pinned our hopes for human research oversight on the belief that getting the Common Rule “right” would help bridge a gap between science and regulation that had grown into a chasm over the last two decades. Not only was this hope not realized, we probably were misguided to think that getting the Common Rule “right” was even possible given the extremely complex political, social, and scientific factors that it needed to address. Perhaps we were naïve to imagine that the federal regulatory process could keep pace with evolving models of science. In retrospect, however, we think the focus on revising the Common Rule may have diverted us from an opportunity to promote more dynamic governance structures, best practices for biobanking, and non-regulatory strategies for promoting patient and donor interests.

According to the Federal Register announcement, the effort to revise the Common Rule, which started in 2011 with an Advanced Notice of Proposed Rulemaking, was supposed to focus on updating the regulations to account for emerging types of science, including large-scale research infrastructure. While the final version of the Common Rule does make incremental progress in addressing these trends, it does not provide a robust framework for the oversight of open-ended research infrastructure and biorepository networks that span institutional and international borders. This really should not have surprised any of us. Regulations are at best a blunt instrument, and they cannot solve every problem.

The regulations have only ever been one piece of the puzzle. From the beginning, institutional efforts to protect human subjects were not constrained significantly by the federal regulatory apparatus. The original Common Rule was written with a focus on the risks posed by interventional clinical research, and called for local IRBs to exercise oversight by applying the federal rules in light of local expectations and values. This framework was premised on an expectation that most research would be hypothesis-driven and local (thus the focus on local values). In this sense, the federal regulations always have been incomplete and out of step with how science works. Accordingly, biobanks and other repositories of specimens and data have had to evolve their own rules and norms. It is time to stop fussing about the Common Rule and consider seriously the other, non-regulatory pathways we have available to advance this important area of human subjects research.

The time is ripe, we believe, to redirect the discourse that for the past six years has focused on the Common Rule revision, to other strategies for protecting human subjects. The relatively narrow and incremental approach to revising the Common Rule constrained dialogue within the bioethics community in ways we should reject. Since publication of the ANPRM, our discussions have focused on the complexity and format of broad consent, the value of secondary use of de-identified samples, and how to balance promoting the research enterprise with donor values regarding consent for specimen collection and use. These questions are, of course, vital to updating the policies that govern human subject research in this country. However, we as a bioethics community have been missing a larger opportunity to engage in a more fundamental dialogue with researchers and research participants. While

we argue about the length and complexity of consent forms or debate whether paper or online communication is more effective, the technological and societal engines that drive research in this country continue to shift toward models of research that rely heavily on institutional infrastructure and cooperation. Although there are a number of smaller research teams and scholars confronting this fundamental shift, we have yet to address these changes as a broader bioethics community.

There are a number of directions we need to explore simultaneously. One important issue is the identifiability of biological samples, and especially the DNA contained within these samples. This was not only one of the most controversial topics raised during the effort to revise the Common Rule; the decision to table this question is explicitly referenced in the preamble to the updated Common Rule. This unanswered question is critical to efforts to build multisite research infrastructure, which frequently depends on the secondary use of data and samples originally collected for other purposes. It is now incumbent on the bioethics community, in collaboration with scientists, health policy experts, and communities of patients and participants, to solve these challenges outside the new regulatory framework.

It also is critical that we expand our efforts to incorporate the views of donors and communities. In contrast with the science envisioned in the 1991 Common Rule, contemporary researchers and research participants are now more likely to view one another as collaborators pursuing a common purpose, thereby casting a new light on the potential role of IRBs. Awareness and concern about the privacy of stored samples and data has grown in response to stories like those of the Lacks family, but also as a result of shifting views about individuals' abiding interest in data and biological samples stored by others. And, closely related, there is an increased recognition of the importance of including underrepresented populations in research, many of whom have, for legitimate reasons, higher levels of mistrust in medical institutions. The revised Common Rule has done very little to address these social dynamics. It is critical, then, that we address how research policies and governance structures can increase public confidence in the integrity of biomedical research and promote community dialogue about issues of common concern to researchers, study participants, and specimen donors. Such efforts could benefit from oversight frameworks that encourage and incorporate community dialogue and emphasize trust-building over institutional procedures and documentation of regulatory compliance. Addressing these concerns is particularly challenging in a networked biorepository setting, where numerous communities are involved as research participants or specimen donors, and researchers may be separated from them both geographically and culturally.

Another challenge we face is the growing development of research infrastructure, including networks of biorepositories that span international borders. There is no universal approach to protecting human subjects that addresses all of the social, political, and regulatory complexities of international collaborations. Can we adopt practices here that exceed the requirements of our new U.S. regulations, but that would prepare us to be harmonized with international models and compliant with international standards to facilitate data sharing? How do we operate above the "floor" of our current regulations so that we are meeting international data privacy standards?

The Common Rule has been amended and it did not solve all our problems. We must “get over it” and move forward. It is time for the bioethics community and other stakeholders involved in research to tackle the important challenges we face by building a new paradigm for human subjects protections, one in which the Common Rule is only part of the picture. This new paradigm will need to account for the complexities of biospecimen and data sharing across large networks, as well as investigator and institutional responsibilities for these kinds of collections. Doing so will necessitate original empirical research about these issues, like the study we are conducting, as well as the development of best practices for governance and oversight at the level of research networks.

Such work is already underway. In recent years, several consortia of researchers and research ethics scholars have joined to develop guidelines and best practices for research, including international research. One leading group is the Global Alliance for Genomics and Health, which consists of 474 organizational members from 42 countries. Promoting these kinds of cross-institutional policies and best practices can allow for more governance structures that balance harmonization across networks with the flexibility to address local donor and community needs. While these processes can be guided and informed by the Common Rule, the development of such structures would not be possible if we were to rely only on the regulatory frameworks laid out in federal regulation.

If we have learned anything from this six-year odyssey with its aspiration to modernize the Common Rule, it is this: we cannot depend on the federal regulatory process to address all the complex governance needs of current approaches to biospecimen research and data sharing. The ethical challenges posed by networked biorepositories sometimes fall beyond legal frameworks or what is possible to address through regulation. To manage these challenges, the bioethics community needs to work closely with multiple stakeholders to develop and refine both regulatory and non-regulatory strategies for modernizing the research enterprise.

Acknowledgments

Funding acknowledgement: This work was supported by the National Human Genome Research Institute (NHGRI/NIH) under award number 1R01HG008988.