INTRODUCTION

Carl H. Coleman

After many years of deliberations, the Department of Health and Human Services (DHHS), along with fifteen other federal agencies, issued final revisions to the Federal Policy for the Protection of Human Subjects (the "Common Rule") in January 2017. These revisions are the first time that the Common Rule has been amended since it was issued in 1991. The revised Common Rule seeks to enhance protections for research subjects while also reducing unnecessary administrative burdens on researchers and research institutions. Shortly before most of the changes came into effect in early 2019, scholars, policy-makers, and other stakeholders gathered for an all-day symposium at Seton Hall University School of Law to critically assess the revisions. The papers in this issue grew out of that event.

One of the chief goals of the Common Rule revisions was to improve the process of informed consent to research, which has widely been criticized as both cumbersome and ineffective. Regulatory changes include the adoption of a "reasonable person" standard for research disclosure, requiring informed consent forms to begin with a "concise and focused presentation" of "key information," and authorizing individuals to provide "broad consent" to future research with identifiable data and biospecimens. The papers by Rebecca Dresser, Nancy M.P. King, and Holly Fernandez Lynch, Leslie E. Wolf, and Mark Barnes examine each of these developments.

Carl H. Coleman, J.D., *is Professor of Law and Academic Director of the Division of Online Learning at Seton Hall University School of Law. He is a former member of the Secretary's Advisory Committee on Human Research Protections (SACHRP).*

Dresser's paper focuses on the introduction of the "reasonable person" standard for research disclosure, which she says has "provoked some consternation among people in the research community."[1] She notes that the standard has a long pedigree in legal decision-making and that many institutional review boards (IRBs) already apply it to their analysis of consent forms, albeit "informally and unsystematically."[2] However, she argues that IRBs are inherently limited in their ability to apply the standard effectively because they are composed largely of research professionals, who lack the perspective of typical research participants. Even when IRB members attempt to put themselves in the mindset of a typical layperson, they are likely to "look to people in their own lives as exemplars of the reasonable person, which can lead to circumscribed and biased conceptions of subjects' informational interests."[3] To counteract these limitations, Dresser urges researchers and IRBs to make efforts "to learn more about what ordinary people want and need to know about the studies they are invited to join."[4] For example, patient advocates and members of the general public could be asked to critique written descriptions of IRB-approved disclosures, or individuals with personal experience as study participants could be invited to participate in the design of consent forms and procedures. "Over time," she writes, "a consensus on reasonable disclosure in different kinds of studies, such as those involving specific diseases, procedures, and investigational phases, could emerge."[5]

The paper by King addresses an issue closely related to the "reasonable person" standard: the requirement to present a "concise and focused presentation" of "key information" at the beginning of consent forms.[6] While the preamble to the final rule provides some guidance on what should be included in the key informa-

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tion section, King notes that it unhelpfully describes the requirement "as simultaneously specific, detailed, and flexible, which is actually a pretty neat trick."[7] In an effort to offer greater clarity, she suggests that the key information requirement should be understood as a mechanism to "focus on the reasons that potential subjects might have for deciding whether to join a study" by highlighting "information that reasonable people who are potential subjects should want."[8] Of particular importance is information that could help dispel the therapeutic misconception, such as details about the nature, magnitude, and likelihood of direct benefit and the distinction between being a research subject and receiving ordinary medical treatment. Like Dresser, King emphasizes the importance of designing consent forms in consultation with members of the general public, particularly individuals who have had personal experience as research participants. For example, she suggests that "a simple exit interview survey could help investigators learn a great deal about how consent forms are understood and about barriers to and facilitators of a good consent form and process."[9]

Finally, in the last paper on informed consent, Lynch, Wolf, and Barnes, provide an in-depth examination of the revised Common Rule's new provisions on "broad consent" to future research with identifiable data and biospecimens.[10] As Lynch et al. explain, in the initial proposal to revise the Common Rule, broad consent was introduced as part of a larger package of reforms that, among other things, would have revised the definition of "human subject" to include all biospecimens, even those from which all personally identifiable information had been permanently removed. Along with other proposed changes — including the near-elimination of the option of waiving informed consent to biospecimen research—those proposals would have effectively made broad consent the only way to conduct secondary research with biospecimens in situations where study-specific consent from the sources of the biospecimens could not be obtained. The final version of the revised Common Rule, however, did not include most of these proposed changes. Instead, it maintained the previous system in which research with anonymous or coded biospecimens falls outside the regulations' purview, and, for research with identifiable biospecimens, IRBs retain the option of waiving informed consent. As a result, Lynch et al. argue that "regulatory broad consent might now reasonably be seen as a solution in search of a problem, a relic of a regulatory innovation that went nowhere."[11]

In light of the alternative mechanisms still available for conducting biospecimen research, Lynch et al. predict that the option of relying on regulatory broad consent will be used only in limited circumstances. They note that option has significant drawbacks for researchers and researcher institutions, including the difficulty of explaining it to potential research participants, particularly when biospecimens are obtained in non-research settings; the fact that if the option of broad consent is offered and refused, the possibility of relying on a waiver of informed consent for future research with those specimens is permanently lost; and the complexity of developing tracking systems to ensure that secondary uses of a sample are consistent with the terms of the participant's broad consent. They conclude by proposing an empirical research agenda to examine how regulatory broad consent plays out in practice.

In addition to reforming informed consent, another major goal of the revised Common Rule was to reduce unnecessary administrative burdens on researchers and research institutions, in large part by reducing the time IRBs spend overseeing low-risk studies. The revisions do this by expanding the categories of research that are eligible for an exemption from the regulations, as well as by specifying particular types of activities that do not meet the regulatory definition of "research." The papers by Lisa M. Lee, Joshua A. Rolnick, Zachary M. Schrag, as well as my own contribution to the symposium, examine different aspects of these changes.

Lee's paper focuses on the revised Rule's exclusion of public health surveillance from the definition of research.[12] As context for this change, she details a lengthy series of discussions between the Centers for Disease and Control and Prevention (CDC) and the Office for Human Research Protections (OHRP) on whether three core public health activities — surveillance, outbreak investigation, and program evaluation — fall into the regulatory definition of research. The CDC took the position that, while most of these activities can be described as both "systematic" and "generalizable," they should not be considered research because they are not "designed" with the production of generalizable knowledge as the goal. For example, an outbreak investigation of a foodborne illness is designed "to stem the outbreak, not to test changes in food handling practices."[13] Such practices, she argues, are analogous to medical treatment provided in the context of a physician-patient relationship, in which any risks or inconveniences are offset by potential direct benefits to the patient. The only difference is that, in the public health context, the "patient" is the community rather than a specific individual.

While the revised Rule's definition of surveillances is different from the CDC's definition, Lee suggests that "it captures the spirit of the activity."[14] Impor-

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tantly, the definition covers not only what the CDC would consider surveillance, but also activities it would characterize as emergency response. Overall, she argues, the exclusion represents "a nod to the conversation of the early days when CDC (and others) argued that while investigating outbreaks, injuries, or risk factors *is* done systematically and *can* generate generalizable knowledge, these activities are designed to address an urgent or important public health problem, not to ask some members of the community to take on risk for the benefit of some unknown others."[15] She notes, however, that unlike surveillance, which is categorically excluded from the regulatory definition of research, public health program evaluation could potentially fall within the definition. While program evaluation might be eligible for one of the exemptions from the regulations, obtaining an exemption "still requires that the investigator submit a document with sufficient detail" to the IRB to make an exemption determination.[16] Therefore, she concludes, while the revised Rule "appropriately limit[s] the scope of the IRB in foundational public health practice activities," it achieves those goal only "in part."[17]

Rolnick's paper explores the revised Common Rule's approach — or, perhaps, non-approach — to quality improvement (QI) activities. He begins by noting three reasons why QI has increasingly come to resemble human subjects research.[18] First, developments in health information technology have facilitated the large-scale retrospective measurement of clinical outcomes, while also making it possible to conduct randomized QI assessments at lower cost. Second, the increasing move away from fee-for-service towards outcome-based reimbursement systems has given health care institutions greater incentives to perform "high-validity" QI, in order to produce results that can meaningfully drive cost-effective care. Third, the consolidation of health care institutions has led to large-scale QI initiatives across multiple hospitals, which are more likely to be generalizable than isolated assessments conducted at single institutions. Despite these trends, Rolnick argues that QI is not the same as research because it has "different organizational and cultural characteristics."[19] In particular, unlike research, QI "is conducted in response to an operational priority, the funding sources tend to be operational rather than grant-based, and the intended audience is more likely to be institutional leadership rather than a community of investigators."[20]

Rolnick is critical of the revised Common Rule's failure to clarify the longstanding uncertainties about the distinction between QI and research. He argues that Rule's continued reliance on whether an activity is "designed to develop or contribute to generalizable knowledge" is not only practically unworkable but also ethically suspect, given that "generalizing depends on context-dependent factors that seem orthogonal to patient risk."[21] In addition, the approach creates disincentives to design QI initiatives in ways that "make it possible to infer causal impact on important clinical outcomes,"[22] as doing so increases the likelihood that the activity will be deemed research, thereby generating additional costs, uncertainties, and delays. In addition to offering suggestions to help QI practitioners work within the existing regulatory framework, Rolnick proposes a new regulatory exclusion for certain types of QI initiatives, which would focus on "activities conducted by a health care system to improve the care they provide to their patients, when those activities do not increase the frequency or magnitude of harms for patients beyond what they would otherwise experience through clinical care."[23]

Like Lee's and Rolnick's papers, my own contribution to the symposium considers the definition of research in the revised Common Rule, but rather than focusing on specific activities like public health surveillance or QI, I raise broader questions about the underlying idea of treating activities that satisfy the definition of research as ethically distinct.[24] First, I argue that the regulatory definition of "research" — an activity "designed to develop or contribute to generalizable knowledge" — is inherently ambiguous. In many cases, there is no clear way to distinguish between activities subject to the Common Rule from activities that are not. Second, I suggest that not all activities that meet the definition of research warrant prospective ethical oversight. While the Common Rule recognizes this fact by exempting specific categories of research from the IRB review requirement, the covered-but-exempt approach is an incomplete solution to the problem of over-inclusiveness, as some low-risk, ethically unproblematic activities are still subject to IRB review. Finally, I argue that some non-research activities raise similar ethical issues as those involved in research, but because of the Common Rule's single-minded focus on research, these activities often take place without any form of ethical review at all. For example, while it is true that public health surveillance is designed to benefit the same community that is exposed to the risks of the activity, that "does not mean that all individuals within the community will benefit equally, nor does it mean that everyone will be exposed to equivalent levels of risk."[25] Thus, it is entirely possible that individuals who are the objects of public health surveillance will be subjected to risks that are not offset by any potential direct benefits, raising the same ethical concern that underlies the requirement for research ethics review.

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In light of these considerations, I argue that the trigger for prospective ethical review should not depend on an "ethically irrelevant criterion like the generalizable knowledge standard."[26] Instead, prior ethics review should be required when some individuals are exposed to greater-than-minimal risks for the potential benefit of others, at least when the activity in question is conducted or supported by federal agencies. Under such an approach, the fact that an activity constitutes research would be neither necessary nor sufficient to trigger IRB review.

Finally, Schrag's paper rounds out the discussion of the revised Rule's changes to the scope of IRB review by focusing on the implications of the revisions for social science research.[27] Overall, he concludes that the revisions "did little to address the concerns about IRB review articulated by social scientists since the 1960s," and that the process of developing the revised Rule "continued the half-century old pattern of treating the social sciences with 'ignorance, haste, and disrespect.'" [28] Schrag acknowledges that the revised Rule contained some "wins" for researchers in the social sciences and humanities, including an explicit exclusion of oral history from the definition of research, an exemption for research involving "benign behavioral interventions," and a "more sensible definition of vulnerable" that no longer suggests "that competent adults might be denied the right to participate in surveys or interviews because of pregnancy or a disability."[29] He also points to a few "non-losses" in the form of draft proposals that did not make it into the final Rule. However, he suggests that these wins and non-losses were outweighed by many disappointments. Some of these disappointments relate to what he characterizes as the revised Rule's excessive reach; for example, he objects to the Rule's continued regulation of "conversations between autonomous adults,"[30] and to the fact that the final Rule failed to incorporate an earlier proposal that would have enabled researchers to begin exempt research without first consulting the IRB. Other disappointments relate to the process by which the revisions were developed, which he criticizes for failing to involve sufficient expertise in qualitative social science, and omissions of procedural protections from the final Rule, such as a right to appeal.

A final aspect of the revised Rule discussed at the symposium was the new requirement for U.S. institutions engaged in cooperative research to rely on approval of a single IRB for any portion of the research that is conducted in the U.S., unless a federal agency determines that the use of a single IRB is not appropriate for a particular context. The single IRB requirement is intended to enhance human subject protection by empowering IRBs to insist on comprehensive protocol changes, while also reducing the time and expense associated with duplicative IRB reviews. Its inclusion in the revised Common Rule represents a sharp break from the original regulatory framework, which emphasized the importance of locally-based ethics oversight.

In light of these considerations, I argue that the trigger for prospective ethical review should not depend on an "ethically irrelevant criterion like the generalizable knowledge standard." Instead, prior ethics review should be required when some individuals are exposed to greater-than-minimal risks for the potential benefit of others, at least when the activity in question is conducted or supported by federal agencies. Under such an approach, the fact that an activity constitutes research would be neither necessary nor sufficient to trigger IRB review.

Edward S. Dove's contribution to the symposium adds an international perspective to the discussion by examining the single IRB requirement in light of his empirical research on regulatory developments in the United Kingdom (UK).[31] Based on that research, Dove discredits one of the primary arguments raised against single IRB review of multi-site research — that it would "exacerbate the withering of local context and local precedents, which are seen as crucial to the ethics review process."[32] He explains that his study of research ethics committees in the UK found that, "rather than local review unpinning diverse ethical viewpoints, values and commitments in research ethics can be remarkably similar across a vast geographic distance."[33] The key to such consistency, he argues, is the existence of "an overarching regulatory structure that works to improve procedural consistency across ethics committees."[34] Thus, he concludes, for the

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revised Common Rule's introduction of a single IRB system to be effective, it should be accompanied by robust regulatory structure that seeks to improve procedural consistency, as well as a stakeholder-led initiative to create "buy-in to drive change in the regulatory approach."[35]

Dove suggests two specific sets of changes that could help the U.S. system move in these directions. First, he calls for replacing the "hub-and-spoke model," in which local sites continue to review and comment on ethics and governance issues in research proposals, even if they have formally designated reviewing responsibility to a single IRB. In its place he calls for a model that leaves ethics issues "solely to the reviewing IRB" and governance issues to administrative offices within local research sites.[36] While recognizing that federal agencies in the U.S. lack the power "to prohibit institutions from conducting their own ethics review of research conducted by their employees and agents," he suggests that agencies can "guide" institutions to a better division of responsibilities through the effective deployment of federal subsidies or "nudges."[37] Second, he argues that greater attention to due process should be incorporated into the single IRB system, including "a managed IRB appeals process" for applicants who are dissatisfied with the judgment of a reviewing IRB.[38]

Together, the papers in this issue highlight many of the key issues that researchers, research institutions, and IRBs will need to consider as they begin the process of implementing the revised Common Rule's changes. I am grateful to the participants in this symposium for such a lively and productive discussion of these challenging questions. I would also like to thank our sponsors, the American Society of Law, Medicine & Ethics, Seton Hall University School of Law, and the Hackensack Meridian School of Medicine at Seton Hall University, for making this event possible.

Note

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