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Requiring a Single IRB for Cooperative Research in the Revised Common Rule: What Lessons Can Be Learned from the UK and Elsewhere?

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Introduction

One of the most significant revisions to the Federal Policy for the Protection of Human Subjects (hereinafter the “Common Rule”),¹ from an organizational ethics and governance perspective, is the mandated transition towards a single institutional review board (sIRB) system that eschews IRB review at multiple research sites (hereinafter the “sIRB rule”). For years, the research community, not to mention a good number of academics, have criticized the regulatory apparatus for review by local IRBs as unfit for purpose in an era of multi-site studies; the apparatus has been viewed as excessively regulating research and thwarting otherwise ethical research projects from moving forward in a timely manner.² The new rule, as announced in the Final Rule published in the Federal Register in January 2017, and which goes into effect on January 20, 2020, generally *requires* United States (US)-based institutions that receive federal funding and are engaged in cooperative research projects (i.e. projects covered by the Common Rule that involve more than one institution in the US) to use the single IRB model for that portion of the research that takes place within the US if certain requirements are met:

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[...]

(b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

- (i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or
- (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.³

Previously, it was discretionary for institutions to have cooperative research projects reviewed by a single IRB. As the Department of Health and Human Services (DHHS) notes, however, rarely⁴ was this

option employed in practice, whether out of concerns of institutional liability⁵ or belief in the value of local review and “local precedents”⁶: “...for federally funded research, most institutions have been reluctant to replace review by their own IRB with review by a single IRB not operated by that institution.”⁷ In consequence, the pursuit of local IRB review at multiple research sites resulted in redundancy and inconsistent outcomes and, it seems safe to say, offered no additional protection to participants.⁸

The sIRB rule aligns in many ways with the NIH Single IRB Policy, which was announced in June 2016 and went into effect on January 25, 2018. This policy “expects” that, subject to a few exceptions, sIRB review will be undertaken for all NIH-funded multi-site non-exempt human subjects research protocols carried out at more than one site in the US.⁹ Beyond aligning with the NIH policy, the sIRB rule also reflects a growing effort by regulators and policymakers in countries around the world (including Uganda,¹⁰ Canada,¹¹ and Australia¹²) to reduce the procedural inefficiencies, redundancies, delays, research costs, and potential for incompatibility of data collected across study sites that have become synonymous with the absence of research ethics review mechanisms designed for multi-site studies.¹³

Nevertheless, efforts at regulatory reform in ethics review systems do not garner unanimous approval. In the US, a number of stakeholders, including IRB members, administrators, and institutional legal counsel, have been opposed to the sIRB rule.¹⁴ Analysis by Holly Taylor and colleagues of public comments submitted to DHHS’s original (in the Advanced Notice of Proposed Rulemaking, or ANPRM, in July 2011) and revised (in the Notice of Proposed Rulemaking, or NPRM, in September 2015) proposal for mandated sIRB review found that support for the mandate was limited: 60% of the respondents were opposed to it.¹⁵ Similarly, DHHS noted that when the sIRB rule was proposed in the NPRM in September 2015,¹⁶ it “was one of the most commented on” across all of the rule proposals to the Common Rule, “receiving more than 300 comments,” and more opposed the proposal than supported it.¹⁷

The sIRB rule is controversial for several reasons. First, it makes single IRB review a uniform regulatory rule that is mandatory in almost all instances, with limited exceptions for the research context. A good number of stakeholders are not partial to this one-size-fits-all approach. Second, it raises concerns about the loss of local review and precedents and specialist knowledge; diminishment of ethical and legal accountability; and a potential increase in risk of legal liability. Third, it raises operational issues such as the need for increased administrative capacity and technological systems to enable sIRB effectiveness; the foremost concern here is the time and effort needed to negotiate reliance agreements among the participating sites. Fourth, the sIRB rule enacts a fundamental change in the ethics review system that has been in place for half a century and with which researchers and regulators were very familiar, flaws included. Was the system really malfunctioning and in need of repair, much less a repair that broadly mandates only one way of doing things?

What, then, are we to make of the sIRB rule? While acknowledging many of the valid arguments raised against the sIRB rule, this article argues nonetheless in support of the mandated transition towards an sIRB system that aims to eliminate IRB review at multiple research sites. I accept as valid the evidence proffered by researchers and policymakers that multi-site IRB review offers no additional protection to research participants and embodies a disproportionate regulatory approach that is inefficient and unduly bureaucratic. My argument unfolds in two parts.

First, I argue that this reform is part of a wider principles-based regulatory objective of the revised Common Rule, which itself is part of an emerging international movement in health research

regulation. This movement advocates *both* robust research participant protection *and* ethical research promotion. Protection and promotion, as we will see, manifests itself in the systems-level design of “next-generation” research ethics review. How regulators are to achieve this two-pronged objective—and whether these should be twined objectives at all—has itself given rise to some controversy. We have good reason to keep a watching brief over this movement in health research regulation, including the ways in which it may be operationalized in an imbalanced manner, viz. *overly* streamlined regulations that seek to promote various forms of health research that come at the expense of participant protection. Yet, I argue that, as principles, protection and promotion reflect sound regulatory design. I ground my argument in legal and regulatory developments in the United Kingdom (UK), which in turn have drawn on regulatory developments in the European Union (EU). In short, the sIRB rule brings the US closer in line with regulatory developments happening in the UK and other countries, and in turn, those developments may provide insight for further regulatory reform in the US. I am mindful, however, of the very different contexts between the US and UK: on the one hand, a federal constitutional system with a panoply of institution-based and private research ethics committees (US), and on the other hand, a unitary constitutional system that has devolved certain powers to some of countries within it and that contains a hybrid system of a small number of region-based and a larger number of institution-based research ethics committees (UK). Nonetheless, the systems share a fundamental common feature: a government-endorsed drive towards mutual recognition of a single ethics review process for human subjects research that is valid across the respective domains of research in which it operates (the research domain overlap between the two systems being biomedical research).

Second, and notwithstanding my general support for the sIRB rule, I draw on my own recent empirical research to highlight several residual—or alleged—weaknesses in the US regulatory structure for research ethics review, and suggest ways in which these weaknesses might be addressed in future regulatory reforms to improve upon the sIRB rule. Here, I investigate one of the main alleged concerns of the sIRB rule—that it will exacerbate the withering of local context and local precedents, which are seen as crucial to the ethics review process. My empirical research suggests that, at least in the UK, there is a *homogeneity* of practice across research ethics committees (RECs), and it might be that concerns about the withering of local context due to the sIRB rule are over-exaggerated. Recent empirical research conducted in the US also suggests that the importance of local knowledge can be overstated (but not necessarily irrelevant).¹⁸ However, other empirical research I recently conducted also suggests that homogeneity (and in turn, greater consistency) of practice—and by corollary, *trust* by stakeholders in the processes and outcomes of a given ethics committee—depends crucially on two inter-related factors: 1) from a more top-down perspective, a robust overarching regulatory structure with committed leadership that works to improve procedural consistency across all ethics committees participating in a mutual recognition system; and 2) from a more bottom-up perspective, a stakeholder-led initiative with committed buy-in to drive change in the regulatory approach. Both a top-down and bottom-up approach are needed to effect robust and sustained regulatory change in ethics review. In the US context, there are grounds for concern about whether such a structure and stakeholder buy-in is firmly in place, even with the sIRB rule now enacted. As part of the second arm of this argument, I also highlight real weaknesses in the regulatory structure for research ethics review in the US that ought to be addressed in future regulatory reforms.

In making this two-pronged argument, I recognize that much prior literature in this area has criticized the *heterogeneous* diversity in IRB decision-making, especially, but not exclusively, in the US. Procedural diversity and inconsistency in decisions are real problems in multi-site research. Yet, in sharing my UK empirical work—where there were also such complaints in past years prior to

regulatory reform—I wish to confound this received wisdom and offer some explanations for these somewhat different findings, and suggest how these are likely linked to structural regulatory conditions underpinning REC/IRB meta-oversight. This analysis will also lead me to suggest further ways in which the US (meta) ethics regulatory system might benefit.

We now turn to the first part of my argument, namely the emerging two-pronged regulatory objective of “protection and promotion.”

The rhetoric and regulatory objective of protection *and* promotion

The impetus behind the sIRB rule for cooperative research projects can be situated within an emerging, international, two-pronged regulatory objective in human subjects research. This objective commands regulators to regulate research with a view towards ensuring both participant protection *and* research promotion. This objective reflects a significant change in the system design of human subjects research. For years, and indeed since the formal creation of the ethics review oversight system in the 1960s, the regulation of human subjects research has been designed to position research participant protection as the primary role of regulators, including the IRB’s role as a local “satellite regulator” of research (at least on the ethical components of the proposed research). Under this system, local IRBs have been tasked with engaging in a precautionary evaluation (or a “regulatory event-licensing” assessment) of the ethics of a research proposal, with a *primary* view towards protecting the health, welfare, and dignity of research participants. The IRB accomplishes this task by issuing a single, independent opinion on the ethical acceptability of a research proposal, set within a regulatory framework that governs their operating procedures and the overall acceptability of research (including its scientific merit and legality). Protection of research participants may have been IRBs’ primary role, but crucially, IRBs have also always performed *secondary* roles. One such role is a variation of the public interest aim of regulators of human subjects research generally: IRBs have an obligation to society, who are often the ultimate beneficiaries of research, to provide stewardship for the promotion of ethical and socially valuable research.

What we have seen in various countries in the past decade or so, however, is a flattening of this role hierarchy in regulatory strategy. A hierarchical role of “protection first and promotion second” has become a two-pronged regulatory objective positioned on equal plane. The introductory summary paragraph of the Final Rule reflects this (re)positioning well: “This final rule is intended to *better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators*. These revisions are an effort to modernize, simplify, and enhance the current system of oversight.”¹⁹ Likewise, in the executive summary, DHHS paints a dichotomous picture of research evolution (a “paradigm shift”²⁰ in how research is conducted) and regulatory stasis: “Since the Common Rule was promulgated [in 1991], the volume and landscape of research involving human subjects have changed considerably. [...] Yet these developments have not been accompanied by major change in the human subjects research oversight system, which has remained largely unaltered over the past two decades.”²¹ In consequence, the regulations for human subjects research were proposed to be “modernized and revised to be more effective.”²² The sIRB rule—reflected in both the NIH Single IRB Policy and in the Common Rule—thus instantiates this desire for “more effective” regulation that evolves *in parallel* with advances in the science it seeks to govern; it is, in other words, seen as fulfilling the two-pronged regulatory objective of participant protection and research promotion. Indeed, the oft-expressed criticism of delay and duplication of multiple IRB review was seen as indicative of a regulatory strategy that emphasized participant protection *at the expense of* research promotion: the regulatory design for ethics review, as crafted in the mid-20th century, may well have been protecting participants, but it came at too great a cost

to research promotion. And one may well argue that a multi-site research study that is subjected to multiple IRB review is not being sufficiently promoted (if at all). What this means is that the “next generation,” 21st century regulatory framework for ethics review commands regulators of human subjects research—including IRBs—to perform their tasks in a way that both protects participants and promotes research. Eliminating or curtailing multiple IRB review for collaborative research is a significant step towards achieving this regulatory objective.

As stated above, the Common Rule rhetoric of protection and promotion tracks rhetoric recently instantiated in statutory regulation elsewhere in the world. We see this foremost in the UK. The Research Ethics Services in the UK are responsible for managing RECs involved in the National Health Services of the UK’s four nations (each nation has its own NHS).²³ NHS RECs, also known more formally as “RECs within the UK Health Departments’ Research Ethics Service,” are more or less region-based committees, which is to say that they are not bound to any institution in the US sense (e.g. a university or academic medical center). Officially overseeing a local health area within the NHS systems, in practice they operate within a centrally administered, national system that enables them to review research applications and provide an ethics opinion on health-related research involving human participants that takes place *anywhere in the UK*.²⁴

The rhetoric of protection and promotion is reflected in the UK’s health and social care reforming Care Act 2014—and operationalized in the mandates of the Health Research Authority (HRA), the regulatory authority for health research in England, and its Research Ethics Service (RES) branch, as well as the mandates of RES offices in the three other nations of Scotland, Wales, and Northern Ireland. The main objective of the HRA in exercising its functions, including the management of National Health Service (NHS) RECs in England (and indirectly across the whole UK), is stated in the Care Act 2014 as two-fold:

- (a) *to protect participants and potential participants in health or social care research and the general public by encouraging research that is safe and ethical, and*
- (b) *to promote the interests of those participants and potential participants and the general public by facilitating the conduct of research that is safe and ethical (including by promoting transparency in research).*²⁵

The Care Act 2014 also charges the HRA with “ensur[ing] that research ethics committees it recognises or establishes [...] provide an *efficient and effective* means of assessing the ethics of health and social care research.”²⁶ Other UK examples of the two-pronged regulatory objective of protection and promotion are seen in HRA guidance for potential members of NHS RECs, which states: “The key duty of a REC is to protect the interests of research participants *whilst at the same time* facilitating ethical research.”²⁷ The RES in Scotland also states this dual role, without specifying a role hierarchy: “The Research Ethics Service in Scotland is a part of the UK-wide national service aimed at facilitating research, *whilst simultaneously* protecting the rights, safety, dignity and well-being of people participating in research in the NHS.”²⁸ Likewise, the RES in Northern Ireland states its mission as: “To protect the rights, safety, dignity and well-being of research participants; and to facilitate and promote ethical research that is of potential benefit to participants, science and society.”²⁹

While the UK has recently instantiated the rhetoric of protection and promotion at the level of statutory law through the Care Act 2014, in practice it has been reflected in regulatory design for a number of years. In this sense, the UK can be seen as a pioneer in positioning protection and

promotion on an equal plane, including through its efforts to reduce multiple REC review for multi-site research projects occurring across the country.

One can trace the modernization of UK research ethics review to 2004, the year the country nationally transposed the EU's Clinical Trials Directive 2001,³⁰ which mandated under Article 6 that EU Member States establish and operate RECs, and charged RECs with the responsibility of giving an ethics opinion, before a clinical trial commences, on any issue requested. Under Article 7, for multi-site clinical trials limited to the territory of a single Member State, Member States had to establish a procedure providing, notwithstanding the number of RECs in its territory, for the adoption of a *single ethics opinion* for that Member State. In the case of multi-site clinical trials carried out in more than one Member State simultaneously, a *single* opinion would be required for *each* Member State concerned by the clinical trial.³¹ This meant that no more than one ethics committee would play a part in assessing the ethics of the clinical trial proposal, no matter the location or number of the site(s) in the country. When the Clinical Trials Directive 2001 was nationally transposed in the UK in the form of the Clinical Trials Regulations 2004,³² the UK decided to make it formal policy that a single REC opinion would hold across the entire UK for *any type of research application* made to an NHS REC, and not only for clinical trials: "The policy of the [UK] Department of Health and the devolved administrations is that the requirement for a single ethical opinion should apply generally to all multi-site research within the UK."³³ The rationale behind this policy decision was that to streamline the regulatory approvals process for all types of health research would greatly reduce the burden and delay for investigators, which by the 1990s and early 2000s was seen by many to be especially pronounced and causing harm to patients and the economy alike.³⁴

Thus, we see that the sIRB rule now positions the US much more closely to the UK and much of Europe, not to mention more similarly constituted federal countries such as Australia and Canada, which have been making concerted efforts to reduce multiple ethics committee review across their states and provinces. This said, as noted in this article's introduction, one must be careful to distinguish both the regulatory contexts and ethics committee contexts of different jurisdictions. NHS RECs, which currently number 85 in total across the UK,³⁵ differ in many ways from the thousands of public and private IRBs across the US, including the mandated scope of review (e.g. only certain areas of health research and research within the NHS), disconnection from any one institution, and their public body nature. The UK, as a Member State of the EU, was mandated under the EU's Clinical Trials Directive 2001 to legislate by 2004 for a single REC opinion for clinical trials conducted in the country; that the UK then extended that mandate by policy to cover all types research reviewed by NHS RECs was possible because of several factors. Foremost, it was possible because NHS RECs are public entities, managed by the four health departments in the UK and subject ultimately to judicial review. The US, by dint of constitutional design, is unable to legislate in a way that comprehensively covers the research ethics oversight of all types of health research for all IRBs. So, the shift towards centralized ethics review, and away from multi-REC/IRB review, is undoubtedly significantly easier to effect in a country like the UK, which is heavily centralized (even with political devolution to three of the four nations) and operates government-managed ethics committees, than in a federal country such as the US or Canada, where ethics committees are institution-based (and therefore as likely to be private as they are public) and states (or provinces) may hold as much (or more) power than the federal government.

Nonetheless, the larger point still holds: the sIRB rule is but the American manifestation of an international health research regulatory objective that has been gestating for at least the past decade. This objective seeks to create a regulatory environment that protects the rights, interests, and welfare of participants in a *proportionate* manner; that is to say, a manner that seeks to make

conducting research easier and less bureaucratic—and thereby more promoted—than regulatory approaches have previously allowed. The sIRB rule fits within the emerging paradigm of protection and promotion. In so doing, it enacts a modification to a long-standing governance structure and cultural practice of research ethics review—namely full, localized IRB review situated in each and every institution involved in a cooperative research project.

It also represents, however—as I have highlighted elsewhere with colleagues—a “modification that carries with it a good deal of uncertainty in its innovation. [...] We are in state of policy equipoise regarding the superiority of the proposed sIRB over the existing system as several performance measures would need to be demonstrated.”³⁶ And indeed, DHHS recognizes this in the text accompanying the revised Common Rule: “We note that the NPRM discussed the fact that data about IRB effectiveness and how IRBs function operationally is generally unavailable.”³⁷ In this sense, then, several of the concerns raised by stakeholders are sound, including concerns regarding operational issues and a lack of evidence of IRB effectiveness (i.e. an assessment of “what works”). As I will discuss below, the sIRB rule does not completely eliminate multiple IRB review, which dampens gains in efficiency. At the same time, we should be mindful of how this “next generation” regulatory approach might be interpreted by regulators at the macro-managing level (i.e. OHRP and the HRA), the meso-managing level (i.e. the UK’s Research Ethics Services and local health boards, and IRB’s institutions), and at the satellite level (i.e. RECs/IRBs themselves). Might the “next generation” balance in approach tilt too far in favor of research promotion? And how would we know when this is the case? Moreover, it is unknown what the long-term impact this two-pronged regulatory objective might have on participants, researchers, and society.

There may not be a need for too much alarm. Findings from empirical research I conducted in the UK suggest that modifications to the health research regulatory space at the levels of statutory law and central regulatory authorities have not so much “trickled down” to affect the day-to-day practices of RECs, as these day-to-day practices have existed for a long and have only recently been enacted in law.³⁸ Ethics committees, managing regulators, and researchers share a common goal of promoting research that is safe and of high quality. There is also a shared commitment to the promotion of research that is ethical and of value of society. Thus, these actors carry similar interests and shared responsibilities, including the achievement of regulatory objectives and working through major moments of transition in the research lifecycle. This said, we should remain vigilant of changing regulatory practices to ensure that ethics committees and managing regulators do not promote research projects at the expense of participants’ fundamental rights and interests. In my view, the sIRB rule does not get this balance wrong, and the evidence indicates that the single REC review policy in the UK has been a success since its enactment in 2004.

In sum, the sIRB rule is a recent example of a general international regulatory trend towards making national and regional ethics review oversight systems built for 21st century science, information communication systems, and ways of collaborating. The sIRB rule follows this trend—it certainly does not buck it—and there are grounds for welcoming it. Having now placed this rule within the larger principles-based regulatory objective of the revised Common Rule, which itself is part of an emerging international movement in health research regulation, the second part of my argument engages more directly with some the main criticisms of the sIRB rule. The first that I address in the following section is that centralized ethics review as envisioned in the sIRB rule, with its hub-and-spoke type of model of a “reviewing IRB” and “relying” institutions/IRBs, wrongfully effaces or otherwise unduly limits local ethics review, which some see as crucial in providing context and knowledge of local research practices. As I suggest through findings of empirical research conducted by myself and others, this may be an exaggerated or misplaced concern.

The red herring argument of local context and local knowledge: insights from empirical research

There is an oft-expressed concern with the sIRB rule (and other attempts at ethics review reform) that is both overstated and misplaced in my view: the concern that it effaces important, if not necessary, local IRB review in cooperative research projects.³⁹ The argument goes that local IRBs reflect, or have more knowledge of, local contexts within geographic areas and/or institutions and/or specific research areas and therefore they are best (or better) placed to opine on the ethics of a research proposal. Undoubtedly, the sIRB rule effects the biggest change to local IRB review in US regulatory history, and fundamentally shifts the argument away from maintaining local review. The case for this shift is expressed in the Federal Register as follows:

The [previous] rule required that each institution engaged in a cooperative research study obtain IRB approval of the study, although it did not require that a separate local IRB at each institution conduct such review. In many cases, however, a local IRB for each institution would independently review the research protocol, and informed consent forms and other materials, often resulting in multiple reviews for one study. When any one of these IRBs would require changes to the research protocol that are adopted for the entire study, investigators would have to re-submit the revised protocol to all of the reviewing IRBs. This process could take many months and significantly delay the initiation of research projects and recruitment of subjects into studies. More importantly, little evidence has suggested that the time and effort put into these activities by investigators (in providing materials to IRBs) and IRBs have significantly increased the well-being of research subjects.⁴⁰

The sIRB rule does not (and indeed cannot) eliminate local IRBs, and it does not address any extra-territorial issues regarding ethics reviews:

The change proposed by the NPRM would apply only to U.S.-conducted portions of studies because the flexibility to make use of local IRB reviews at international sites should be maintained. It might be difficult for an IRB in the United States to adequately evaluate local conditions in a foreign country that could play an important role in the ethical evaluation of the study.⁴¹

The argument in favor of local IRB review is long-standing and should not be taken lightly. Since the creation of the IRB system in the 1960s, some policymakers have argued that norms or values do not transcend borders, including institutional borders. In many ways, the IRB system in the US is the most decentralized regulatory system ever devised. In 1967, Surgeon General William Stewart explained that:

It is the feeling of the [Public Health Service] that local groups will have a much closer rapport with their communities and a better understanding of the meaning of such terms as privacy and confidentiality to differing local populations. This approach should not only provide greater protection for the subjects but assure more productive research. An additional principle is also involved. If the research program financed by Federal funds but conducted in academic institutions and nonfederal research institutions is to remain vigorous and effective, the individuals conducting that research and the officials of the institutions in which it is conducted must recognize and accept their responsibilities in the use of Federal funds. It is, therefore, our position that the institution should wherever feasible play the major

role in administering its own research under prevailing local mores and conditions following general guidelines given by us.⁴²

This argument and belief persisted into the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the late 1970s:

The Commission believes that the rights of subjects should be protected by local review committees operating pursuant to federal regulations and located in institutions where research involving human subjects is conducted. Compared to the possible alternatives of a regional or national review process, local committees have the advantage of greater familiarity with the actual conditions surrounding the conduct of research. Such committees can work closely with investigator to assure that the rights and welfare of human subjects are protected and, at the same time, that the application of policies is fair to the investigators. They can contribute to the education of the research community and the public regarding the ethical conduct of research. The committees can become resource centers for information concerning ethical standards and federal requirements and can communicate with federal officials and with other local committees about matters of common concern.

[...]

In its deliberations, it is desirable that the IRB show awareness and appreciation of the various qualities, values and needs of the diverse elements of the community served by the institution or in which it is located. A diverse membership will enhance the IRB's credibility as well as the likelihood that its determinations will be sensitive to the concerns of those who conduct or participate in the research and other interested parties.⁴³

And the argument in favor of local IRB review continues to be expressed in the writings of many scholars today, such as Brian Gladue of the Office for the Protection of Human Subjects at the University of North Texas Health Science Center, who writes:

Each IRB operates within a community and is expected to address ethical research issues within that specific local community of scholars, scientists, citizens, and research subjects. Thus, a research project that is approvable "as is" in one university might raise an ethical eyebrow at another. Although this raises no shortage of frustrations among scientists dealing with multiple IRBs in inter-institutional research projects, there is a strange strength in this concept. By encouraging each IRB to become educated and aware of what works and does not work within their specific operational area, each IRB is actually more in tune and in touch with the spirit as well as the printed regulations of ethical research than would happen with a top-down compendium of dictums from the central government. Just as "all politics is local," all ethical reviews are local.⁴⁴

Yet the case for local IRB review rests more on the force of its rhetoric than on the force of its logic. Appeal is often made to the close connection between an ethics committee and an abstract "local community," but evidence of whether such a rapport or connection actually exists, whether local IRBs have any "greater familiarity with the actual conditions surrounding the conduct of research"⁴⁵—and whether this adds any value to an ethics review—has not been forthcoming. More broadly, it is unclear why ethics reviews are seen as engaging exclusively local or even national concerns, particularly in present-day biomedical research that is colored by inter-institutional, inter-

regional, and international collaboration. Compared to science review, ethics review is an exercise in localized assessment *ad infinitum* and *ad absurdum*. Peer review bodies for science are often conducted at one site, such as the location of the funder or sponsor, wherever they might be in the world. This is because there is general acceptance that a universal language of science exists, grounded foremost in methodology and consideration of the proposed research's relationship to similar previous studies and their findings.

Does ethics review lack a similar universal language? Ethical issues undoubtedly vary, depending on the research in question, and indeed to some extent on the location of the research site(s), but the ethical framework that committee members bring to bear on a project should not depend in itself on their institutional and geographic position. The question arises as to what exactly constitutes ethical values and commitments particular to a local context, and how such values and commitments are divined through the collective ethical reasoning of an IRB. Ethical reasoning may be conducted at various levels of systemization: from the highest level of abstraction—theories—and from there to principles (e.g. respect for persons, beneficence, non-maleficence, justice), to rules or norms (e.g. good research design, competent investigator, favorable balance of harm and benefit, informed consent), which in turn yield ethics judgments. In theory, each IRB member, and the IRB's collective opinion, may appeal to and apply a spectrum of theories, such as principlism, casuistry, deontology or utilitarianism, not to mention pragmatism, each of which may consist of a systematic corpus of principles and rules. This is why it is not uncommon for IRBs (and members within them) to reach different opinions on the same research proposal—just as with courts of law, there can be a range of reasonable opinions. Within this spectrum of theories, different outcomes may emerge. None, some, or all may speak to issues regarding a specific geographic or institutional context.

The language of ethics and the ethical imaginary should enable IRB members individually, and the IRB in aggregate, to reach an “opinion” and justify that opinion by referencing, explicitly or implicitly, wider, socially-accepted norms or values. More often than not, though, those norms or values transcend borders, as seen in the CIOMS International Ethical Guidelines for Health-Related Research Involving Humans⁴⁶ and the WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants.⁴⁷ For example, the value of autonomy and the principle of respect for persons is reflected in the general requirement for informed consent in most forms of biomedical research. A local IRB at a university department will not (or should not) disregard the importance of informed consent as compared to its neighboring IRB at the academic medical center across town. I accept that some norms and values may be more emphasized than others, depending on cultural contexts. It may be the case, for example, that the trope of the liberal individualist ethos in the US that is reflected in, among other things, a strong demand for individual and written informed consent, carries less credence within certain communities in certain parts of the country. Some scholars may argue that informed consent may not fulfil the same important role in some contexts, as the concept is grounded in an individualistic ideal of personal autonomy. But it does not necessarily follow that local IRBs would know this “local context” information, would know this information better than another IRB, that this information necessitates or should necessitate a change in research design, that this information should modulate the ethical viewpoint of the IRB members, or that in the case of a cooperative research project such information cannot otherwise be obtained and considered by the sIRB. The rationale for preserving ethics committee review in each institution (and within each institutional department) is no more justified than it is for preserving ethics committee review in a region. Values and commitments in research ethics need not be bound to, nor defined by, a geographic border or institutional walls.

Preservation of institutional sovereignty for local review of multi-site studies carries heightened risk of several regulatory drawbacks, including inconsistent, sometimes overly risk-averse, and unjustified local interpretations, and confusion about the standards for compliance that apply to different types of research. On this point, much of the literature on the ethics review system, especially in the US, has been critical of the heterogeneous culture and decision-making practices in each ethics committee. “Inexplicable variation is a persistent pattern” among IRBs; they are “consistently inconsistent,” Carl Schneider writes in his book criticizing the “misregulation” of human subjects research.⁴⁸ Not only can individual IRBs and IRBs within one institution fluctuate in their decisions, but multi-site studies also run an increased risk of having “inconsistencies” between IRB decisions, which may contradict each other.

I do not refute the evidence that has accumulated for years that inconsistency is a real issue in both IRB practices *and* outcomes, and that the concern for most focuses on the latter.⁴⁹ Nor do I deny that “local context” will probably wither to some degree under the sIRB model—that is partly the point of the regulatory change. But there is also evidence from the UK and elsewhere that confounds this received wisdom of the value of local context: rather than local review unpinning diverse ethical viewpoints, values and commitments in research ethics can be remarkably similar across a vast geographic distance. I want to suggest that this alternative finding is linked to structural regulatory conditions underpinning REC/IRB meta-oversight, particularly an overarching regulatory structure that works to improve procedural and substantive consistency across ethics committees.

Over the course of 2016, I conducted a socio-legal investigation into the roles and practices of NHS RECs in light of recently implemented health research regulation in the UK that explicitly seeks to promote health research in the country, in part by streamlining regulation itself—for example, by instituting ‘proportionate’ ethics review for some types of research to accelerate the review times and overall time that a research study could get underway. It was unclear how these recent regulatory changes, stressing efficiency and maximization of UK competitiveness for health research and maximization of return from investment in the UK, might affect the procedural and substantive workings of NHS RECs. It was also unknown whether the modification of research regulation at the level of legal architecture to promote research “trickled down” to the day-to-day practices of RECs, which the HRA is responsible for managing directly in England and partially across the UK.

Given the common finding of inconsistency within and between ethics committees, I expected a similar finding in my naturalistic observations of REC meetings. To the contrary, I found that a common behavior existed across the five RECs I observed for one year, and such behavior did not seem to impact on the resultant ethics opinions. As in the US, relative to each other, RECs are “black boxes”: committee members note they have little interaction with other RECs and have few common opportunities to engage with other RECs—and nor do they have much desire to do so. They do not really know what other committees do, whether they undertaken ethics reviews in a similar manner, and whether their ethics opinions are similar to their own. Yet, despite these black boxes existing between each other, there exists a surprising degree of *group homogeneity* in terms of approach and rituals.

In the UK, one of the key rituals is the meeting and agenda structure for RECs. Established by the HRA in a template form, the meeting agenda was consistent across all five RECs I observed, namely in the order of: 1) Apologies for Absence; 2) Minutes of the Meeting Last Held; 3) Matters Arising; 4) Items for Information and Discussion; 5) REC Manager’s Report; 6) Declarations of Interest; 7) New Applications for Ethical Review led by the Lead Reviewer and then Second Reviewer; 8) Any Other Business; and 9) Date of Next Meeting.

Within this structure, the timing was consistent, too. Items 1-6 rarely extended beyond five minutes discussion in total. The vast majority of each meeting was dedicated to Item 7: New Applications for Ethical Review. Following the presentation by the nominated “Lead Reviewer” (which typically ranged from seven to 15 minutes), the nominated “Second Reviewer” would then add a few comments (which typically ranged from three to seven minutes) in a gap-filling manner, raising further queries to be posed to the chief investigator or areas of concern within an application. Then, the REC Chair would invite other REC members to comment on the application. Following this open discussion, the REC Chair would write down the “main issues” to discuss with the chief investigator or his or her representative, assuming the chief investigator or representative was attending in-person. (REC Managers were always taking minutes of the meetings, portions of which were then transformed into opinion letters that would be sent to the chief investigator and his or her research team.) Once the list of questions was formulated to all members’ satisfaction, the REC Chair or Manager would retrieve the chief investigator waiting outside, invite him or her inside, and ask questions regarding the application. Following this back-and-forth dialogue, the chief investigator would leave, and the REC Chair would invite members to deliberate further on the application, culminating in a decision. More often than not, the outcome would be a “provisional opinion,” whereby the REC would request further information from the research team before reaching a final decision (which would almost always be a favorable opinion).

With an array of rituals, individual member and committee idiosyncrasies (e.g. the seating pattern, organization of papers, ways of communicating), and moral intuitions, even if ethics is “situated”—constrained by the limits of the committee structure, the communicative and epistemological dominance of the medical and scientific expert members, or the desire for group consensus and efficiency—any given ethics committee’s output, as with the input, is somewhat uncertain. But only somewhat. For example, certain cues in the course of an ethics review (e.g. the type of research under review, a REC’s trust in the researcher, the quality of the submitted application) can help make an outcome more predictable, though not certain. There is always an element of uncertainty in the outcome of an application following an ethics review. As regards precedent, intra-REC precedent (i.e. comparing current applications to past applications and decisions) occasionally was invoked in the deliberations I observed to serve as a reference and maintain consistency, but this was not done systematically. One member told me he could only recall two instances in over 20 years of serving on a REC where precedent was invoked. The norm was that each application was reviewed on its own merits. Group experience, or a “memory within the group” as one person told me, predominated the aiding of a decision at a higher thought level. As one REC Chair phrased it, “group moral maxims that we all generally share” helped determine if the past opinions were relevant to the current application so as to apply like a generally accepted ethical principle. Collective memory and experience, along with these “group moral maxims,” maintained order and propelled the REC towards a decision that they believed would be consistent within their REC and, ideally, across others, too.

What drove this homogenous REC group culture across the five I observed may be in large part due to HRA standards driving consistency across the UK. Though the 300-page REC SOPs that the HRA publishes place a good deal of procedural standardization on RECs, they nonetheless permit them a wide latitude in which to roam substantively on ethics. And this wide latitude *can* result in potentially differing outcomes. For example, Samantha Trace and Simon Kolstoe conducted an analysis of the outcomes of several “Shared Ethical Debate” (ShED) exercises undertaken by some NHS RECs in England, with the resulting minutes from each REC compared along with the final decisions made by each REC on the project under consideration. They found that, “[b]roadly speaking, NHS RECs have been getting more consistent over time in terms of their decision-making,

but the reasons for the final decisions as described in the committee minutes continue to vary widely.”⁵⁰ They suggest that qualitative research needs to be done “to understand why different committees can have such different discussions in relation to exactly the same research project and yet come to essentially the same conclusion.”⁵¹

I would attribute this similarity in outcome (i.e. conclusion) and variation in discussion (at least as reflected in the minutes, which must be taken with some caution) to the wide latitude given to RECs to roam on substantive ethical discussion. Even so, in my observations, on the whole RECs appear to roam in similar ways and in similar spaces. None exhibited practices and outcomes that could be seen as falling outside a range of reasonableness. More intriguingly, elements of REC culture—interpretive flexibility, self-policing behavior, and sensitivities with regard to relationships with researchers—would ordinarily suggest heterogeneity and militate against homogeneity. And yet, a strong degree of group cultural and regulatory homogeneity exists. Importantly, an “ethics of space” existed for each REC I observed that also constituted a connected regulatory space of RECs across the UK where homogeneity reigned. In other words, a researcher in the UK can submit an application in the south of England or the north of Scotland and experience a startlingly similar ethics review. RECs themselves may not be aware of how similar they are, procedurally and substantively. More than once REC members asked me how their REC “compared” to the others I was observing, and whether I found any differences. As I responded to them, at least based on the five I observed, the procedural and substantive differences are few and far between. Despite, or perhaps because of this homogeneity, there is a strong desire by RECs, including REC Managers, to preserve the sanctity of their black box and ethics of space. The evidence from the UK suggests, then, that it is possible to achieve procedural and substantive consistency across ethics committees without a concomitant withering of local concerns—provided, however, the right system and structure is in place and trust across committees is sustained.

Other empirical research carried out in 2015 and 2016 also reinforces this finding, albeit from a different angle, namely an international angle that focused on concerns regarding multi-jurisdictional data-intensive research projects.⁵² Here, I conducted interviews with 25 international experts in research ethics on the topic of ethics review “mutual recognition.” The aim was to explore the issues associated with ethics committee review of international data-intensive research projects, identifying current problems, real-life experiences, and potential solutions that are both bottom-up (via researchers, participants and publics) and top-down (via statutory regulation), as well as challenges in achieving both.

The most significant challenge identified by the participants was the pervasive notion of “locality,” specifically the sticking point of the desire by many in the system to protect local context and sensitivities. How, I wondered, could we address this ongoing concern that ethics is somehow necessarily “local,” and must remain local—nationally and institutionally—even though evidence suggests that a) ethics review processes and ethical reasoning is (or can be) similar across walls and borders, and b) with the right regulatory structure(s) in place, multiple reviews can be eliminated without prejudicing the rights and interests of research participants?

Some interviewees emphasized that existing and engrained procedural difference is often invoked as a rationale for local review, but felt it was “[not] defensible to maintain procedural differences because it’s just that you do things slightly differently. [It’s] just a nonsense to say that that should stand in the way of a more efficient review.”⁵³ Rather than accept local context as a valid justification to avoid reforming the ethics oversight system, participants suggested that existing initiatives in several jurisdictions demonstrate that it is possible to have a model similar to the sIRB rule, even without a centralizing authority such the UK’s HRA that can drive procedural consistency

through mandated SOPs and other regulatory devices. For example, Canada, like the US, has institution-based ethics committees, known as Research Ethics Boards (REBs). Multi-jurisdictional ethics review reform has been slow-going in the country. Yet several interviewees in Canada noted that Clinical Trials Ontario (CTO) provides an example of how ethics review can be rationalized in a sound way. CTO provides a single Ontario-wide ethics review for multi-site clinical trials in the province. The CTO Streamlined Research Ethics Review System (SRERS) supports any single “CTO Qualified” REB in Ontario to provide ethics review and oversight for multiple research sites participating in the same clinical trial. The aim is to scale up the initiative to other provinces.

In sum, what both the UK and international empirical research indicates is that the emphasis on the importance of local review and local context may be misplaced or exaggerated. It is unclear what “local context,” “local knowledge,” and sensitivities entail from an ethics perspective (as opposed to, say, from a governance or operations perspective), and it is doubtful whether IRBs can ever be comprised in a way that involves or represents local communities in ethics review processes in a meaningful way, much less that IRBs can adequately represent context and sensitivities through the voices of its (generally very few) community members. Perhaps what really is at stake here in this criticism of the sIRB rule is the desire to maintain local institutional control (and on this point, Gladue’s connection between local politics and local ethics is apposite), and the rhetoric of local context is the hook on which to place this desire. Local control, however, is not a sufficient justification to ossify the regulatory system. The shakiness of the local context argument is one of the principal reasons in my view that the sIRB rule ultimately prevailed.

Though the local context criticism is in the end more of a red herring, there are two real weaknesses that exist in the sIRB rule that demand attention.

Residual weaknesses in the sIRB rule

Though I argue in support of the sIRB rule, two residual weaknesses remain in the regulatory structure for research ethics review that the Common Rule reform does not address:

- the hub-and-spoke model of a “reviewing IRB” with “relying” institutions/IRBs dampens the gains in efficiency the Common Rule claims to achieve with the sIRB rule (Weakness 1); and
- IRBs act as administrative regulatory bodies, so principles of natural justice (in other words, key elements of due process) should apply, and yet they are not fully built into the regulatory structure (Weakness 2). This weakness is expressed most prominently in the ongoing need for an IRB appeals system, which is all the more important with the implementation of the sIRB rule.

I suggest that these two weaknesses are not fatal to the sIRB rule or the revised Common Rule, and as such in the following sections and conclusion I suggest ways in which they might be addressed in future regulatory reforms.

Weakness 1: the hub-and-spoke model

The sIRB rule stipulates at § __.114 that “...an institution [...] that is engaged in cooperative research [...] *must rely upon approval* by a single IRB... [.]”⁵⁴ The accompanying text published in the Federal Register states that: “Institutions may still choose to conduct additional internal IRB reviews for their own purposes, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule.”⁵⁵ The concern here is that the language of “rely upon” in § __.114 is ambiguous; the hub-and-spoke model underlying the sIRB rule, whereby the “hub” reviewing single IRB “approves” (or not) a research proposal, may not make much difference in

reality as the “spoke” IRBs connected with the relying institutions likely are to still conduct local ethics reviews. And indeed, this should not be too surprising if the regulatory system enables power to stay with the local institutions. The language of the sIRB allows for too big a loophole for local IRBs to engage in ethics reviews, even if they lack regulatory status in terms of compliance with the Common Rule. The “sIRB” may be a misnomer, then, as there is unlikely to be just one single IRB involved in the process; “central IRB” seems more a fitting label for the model espoused in the Common Rule.

A similar concern arose in the UK when the country moved to a system of “multi-center RECs” (known as MRECs) in the 1990s. In response to long-standing and vocal concerns from the research community (and others) about the duplicative and inconsistent ethics reviews with multi-site studies conducted by “local research ethics committees” (known as LRECs), which were required for each local health authority boundary in which the research was being conducted (e.g. a hospital or university), in 1997 new Department of Health guidelines sought to simplify the procedure for the ethics review of multi-site studies. The new rule (HSG(97)23⁵⁶) required research studies conducted in the UK that involved four or more LREC geographic localities (i.e. four or more health authority boundaries) to have approval from *both* a single MREC in the country (out of 13 that eventually existed), and the LREC for each participating site. As a Department of Health document stated, the rationale for the MREC creation was to *streamline* research governance processes to improve the environment for clinical trials:

...[the] reasons for streamlining the system for LREC review of multi centre trials [...] [are] [...] to contribute to improved clinical outcomes by approving potentially beneficial research more efficiently [...], to reduce delays to good research [...], [and] [...] to avoid a large number of LRECs all devoting time to the same aspects of identical protocols.⁵⁷

The MREC system was overseen by the NHS Research and Development Directorate (and was directly accountable to the Department of Health), whereas LRECs were overseen by regional health authorities. Research could not proceed until each LREC informed the approving MREC of its lack of objection with respect to “locality issues,” a term that was later specified in the first edition of the *Governance Arrangements for Research Ethics Committees* released in September 2001. This meant that LRECs could provide advice about the local acceptability of a protocol and could reject the research protocol for “locality issues,” but could not amend the study protocol or the study instruments. One MREC approval would be valid throughout the UK; if the MREC declined to give a favorable opinion on the application, any existing approval by LRECs still stood, but those LRECs had to be informed of the MREC’s decision.

Despite this regulatory change that was intended to smooth approvals for multi-site research, many researchers found that in practice, MREC approval did not necessarily lead to more efficient and cost-effective LREC approval.⁵⁸ As one UK expert in research ethics has written:

Many local RECs did not trust these newly-formed MRECs and were unhappy to relinquish their perceived responsibility for the *ethical* review of research projects taking place within their patch. This often resulted in lengthy delays whilst LRECs and the MREC disagreed over *ethical* issues occasionally resulting in the local REC refusing to approve the study for their local site.⁵⁹

In 2004, in response to the criticisms of the clunky MREC system and, in line with the coming into force of the Clinical Trials Regulations 2004 that mandated a single REC opinion across the entire UK for clinical trials (and later by policy extended to any type of research application made to an NHS

REC), MRECs were abandoned. Since 2004, the UK has reverted to its (L)REC approach whereby each NHS REC is in some sense local to an area health authority, but has jurisdiction to decide and apply a country-wide ethics opinion.

We can also look to a recently published empirical study in the US that suggests the hub-and-spoke model may be deficient. Diamond and colleagues undertook an observational study to examine the impact of the NIH policy of sIRB review on time and efforts required to initiate clinical trials by the National Institute of Child Health and Human Development (NICHD) Cooperative Reproductive Medicine Network.⁶⁰ They found that sIRB reviews for multi-site trials reduced the time for IRB review and initial approval, but *increased the total time* to final local site approval. Indeed, they found that under the sIRB system, the total amount of time before the study could start almost doubled. The reasons for the delays varied, but included individual sites frequently requiring additional time for local IRB amendment submissions. Institutions differed in the language they used concerning areas such as HIPAA⁶¹ (i.e. health privacy legal protections), participant injury, indemnity, privacy and compensation, biosafety, radiation and chemical safety, local processes and approvals for adding or removing study personnel, conflicts of interest, and advertising of studies through different media.

There are three lessons to impart here. First, past experience indicates that it is exceedingly difficult for local reviewing ethics committees to cede their power to review unless law or regulation clearly disincentivizes their undertaking such reviews. If the legal or regulatory language is ambiguous, there is little hope that overall review times and lead-in time before the research gets underway will improve, and the risk of inconsistency and bureaucratic delay will remain unsettlingly high. Second, past experience suggests a need for enhanced coordination among IRBs—if not harmonization of forms and processes—and more guidance from regulatory authorities such as OHRP and funders such as NIH that address the function and expectations of individual participating sites.

Third, and more critically, the hub-and-spoke model and the past MREC experience in the UK suggest that there is a problematic entanglement of, and confusion between, ethics and governance. I have argued above that the purpose of an ethics committee is to ensure that any anticipated risks, burdens, or intrusions will be minimized for the participants taking part in a research study and are justified by the expected benefits for the participants or for science and society. The subject matter that forms the basis of this assessment is centered on rigorous analysis of ethics issues: whether the dignity, rights, safety, and well-being of participants are properly protected and promoted through, *inter alia*, the study design, the collection and use of personal data, the consent process, and research outputs. Such an assessment differs from one that assesses the governance issues of the local study sites. Governance issues should *not* be part of the remit of an ethics committee, but rather the remit of another body with proper competence to assess these matters for the local site. Such matters would include the determination of proper qualifications of the study team members; oversight, report, and management of conflicts of interests; biosafety, radiation safety, or chemical safety issues; data storage assessment; cost coverage analysis; financial review; review of plans for data protection and local institutional HIPAA language/compliance (especially in the consent form); and requirements for specific wording in either the protocols or consent forms that may vary by institution or by state (e.g. subject payment, subject injury and compensation, indemnification, advertising, etc.). These governance issues should be excised from the remit of an IRB and placed instead in an R&D office, research governance office, human research protection program, or a similar body. Doing so would enable ethics committees to focus on their main task of ethics review and would facilitate a model that actually establishes a single IRB to undertake the ethics review of a multi-site study. It would also perhaps signal to the relying institutions that they should strive to be

flexible in their governance arrangements to promote harmonization and avoid lengthy and often unnecessary delays in approving multi-site research studies.

Weakness 2: deficient due process

Another remaining weakness in the sIRB rule, and more broadly in the IRB system as a whole, is the absence of fundamental elements of due process. Specifically, I am speaking here of the lack of an appeals process for applicants when their application is not approved—either through outright rejection or some “provisional” outcome with a demand for further clarification by the applicants. This is a long-standing concern in the US IRB system that the sIRB rule does not resolve. It is more concerning within the sIRB rule, however, as the rule seeks to channel the ethics review process into one IRB, which will act as the sole and final arbiter for the review. It therefore increases the risk that there will not be another competent body to which an applicant may lodge an appeal.

Carl Coleman has argued that IRBs’ approach to risk assessment, and perhaps their work more broadly, closely mirrors the deliberative process used by common law juries:

...the process of jury deliberations exhibits many of the same characteristics as IRB decision-making, including reliance on general, impressionistic judgments unsupported by specific reasons; the absence of any obligation to explain or justify decisions; a focus on individual cases rather than general principles or rules; and the potential for inconsistent determinations in similar situations. Juries are also justified by the same values of localism and community input that underlie the current system of IRB review.⁶²

While not disagreeing with this characterization, I would posit that IRB members, because of their duty to attend to the process of their decision-making as well as to the substance of their decision, could also be likened to non-stipendiary magistrates (i.e. justices of the peace) in the criminal justice system, or more directly, as administrative regulators who issue licenses.⁶³ On this claim, Carl Schneider convincingly argues that IRBs engage in a “regulatory event licensing” system:⁶⁴ they must examine every study in advance, and without the favorable opinion from an IRB, research simply cannot proceed, either by way of law, policy, or practice. Given that IRBs are bestowed with authority through law and regulation (and perhaps also institutional policy) to pre- or proscribe the choices and actions of researchers, and to judge whether and on what terms research conforms to ethical and social standards, we ought to look at comparisons with quasi-public decision-makers who perform a similar function. In so doing, we see that they share the characteristics of many (quasi-)legal tribunals or public administrators. Just as those tribunals and public administrators are bound by principles of due process, so too ought we to expect principles of due process to apply to IRBs. As IRBs engage as regulators of ethical research conduct, and the Common Rule is a form of regulation, we must consider key elements of “good regulation.” Few would dispute that one element is that regulators use procedures that are fair, accessible, and open.⁶⁵ IRBs, and the overarching systems governing them, should treat applicants equitably and subject them to a fair process of ethics review. Moreover, establishing and following clear procedural rules protects the IRB process and IRB members from accusations of bias, unreasonableness, arbitrariness, and inconsistency.

As Holly Fernandez Lynch has argued, IRBs could stand to become much more transparent: “Given the clear benefits of IRB transparency in terms of accountability, consistency, trust, and efficiency, the question is not whether to push for improved transparency or why, but rather how and along which parameters.”⁶⁶ Fernandez Lynch proposes that among the mechanisms that IRBs could

implement are verbal communication, written communication, open IRB meetings, accessible meeting minutes, accessible IRB determinations, and accessible IRB websites and training tools.⁶⁷

In the context of ethics committee review, I would extend Fernandez Lynch's mechanisms of transparency by advocating IRBs adopt fundamental elements of due process. These would translate as a right to be heard (e.g. voluntary but encouraged attendance of applicants at IRB meetings to provide additional information and to answer questions); a right to receive a timely, reasoned, ethics-based, and understandable decision; and, most importantly, a right to appeal a decision.⁶⁸ Such an appeal may be on the grounds that the decision was not made appropriately within the procedural rules of the IRB, or that the decision was unreasonable, in as much as no reasonable committee could have reached the same conclusion.⁶⁹

By way of comparison, there is a managed appeals process for NHS RECs in the UK. Where a REC has given an unfavorable opinion on an application for ethics review, the applicant has the following options for seeking further review: (i) they may submit another application to the same or different REC, which should be reviewed as a new application; (ii) they may appeal against the decision of the first REC and seek a second opinion from another REC on the same application; or (iii) a request may be made to vary the opinion where it appears to be based on error or misunderstanding (e.g. error or misunderstanding in relation to the application or the further information provided by the applicant or advice from a referee; interpretation of relevant legal or regulatory requirements; or the application of other published guidance to the conduct or management of the study).⁷⁰ Under the first option, where the application is being reviewed by a different REC, the REC Manager (i.e. administrator) of the second REC can contact the REC Manager of the original REC to request a copy of any correspondence relating to the previous review. This may include the unfavorable or provisional opinion letters if these have not been provided by the applicant. All relevant correspondence is expected to be included with the documentation submitted to the REC members for review at the meeting.⁷¹

The NHS REC managed appeals process is not easily transposed to the US IRB context, especially due to the institutional nature of the latter's regulatory design. Here, an appeals process can be managed through a special masters or agreed-upon arbitrators – a panel of research ethics experts who are independent of any of the institutions in the cooperative research project – mutually agreed upon and stipulated in a reliance agreement. This would avoid appealing to another IRB at the same or another institution, which would raise potential political and legal disputes. Such a panel would be enabled to review any appealed decision or other cases of a dispute. In the longer term, it may be desirable to implement independent, stand-alone, standing appeals bodies for IRB decisions – perhaps on a regional basis (similar to the Court of Arbitration for Sport); such an agreement may be established between a select number of institutions (e.g. the top 20 most research-intensive universities and academic medical centers) on a pilot level. In the interim, though, it seems that an arbitration mechanism established through reliance agreements are more feasible and in furtherance of due process procedures.

In sum, neither the sIRB rule nor the revised Common Rule incorporates fundamental elements of due process that should obtain in the ethics review process. While research applicants now have the opportunity, in principle, to have their proposal approved by just one IRB, it remains the case that they do not have an opportunity to be heard, to receive a written and reasoned decision, and to appeal an unfavorable opinion. By channeling the ethics review process into a single IRB, the sIRB may exacerbate these concerns of due process by curtailing the ability of researchers to seek and appeal to another IRB that may have more transparent and fair principles of procedure. As with the hub-and-spoke model weakness discussed above, this weakness of deficient due process is not fatal

to the sIRB rule: both can be remedied. But it will take committed leadership from those at the top wielding regulatory authority, and it will also take committed buy-in and stakeholder-led initiative from the bottom up.

Conclusion

In this article, I have argued generally in support of the mandated transition towards an sIRB system that aims to eliminate IRB review at multiple research sites. The benefits of the sIRB rule are that, *inter alia*, it 1) aligns with a larger regulatory movement in human subjects research driven by proportionality that seeks to protect research participants while also promoting ethical research; 2) signals sensible and proportionate reformed regulation of research; 3) works around the red herring of the local context and precedent claim; and 4) should, on the whole, increase efficiency and achieve a better balance of research promotion without any detrimental effect on the rights, interests, and welfare of participants. Undoubtedly, implementing the sIRB rule has been no easy feat. IRBs have always been bodies of power that control research, and ceding control and placing trust in another IRB and institution is far from simple; it is unsurprising that some IRBs and their institutions have been reluctant to cede some of their power and control as a result of the sIRB rule.

At the same time, the sIRB rule is a good, but not perfect, rule. Among the weaknesses highlighted in this article are that 1) the hub-and-spoke model may not actually lead to tangible benefits in timings and savings as it allows for too much power within local, relying IRBs and institutions to review and comment on both ethics and governance issues in a research proposal, and 2) the elements of due process remain unfulfilled, especially the right of a research applicant to an appeals process. Both of these weaknesses can be remedied through further, future regulatory reform.

Regarding the first weakness, the hub-and-spoke model can be modified to better bifurcate ethics and governance issues, leaving the former solely to the reviewing IRB and the latter to R&D or administrative offices of the local sites, which are best placed to comment on them. One option to achieve this could be through further guidance promulgated by OHRP (i.e. regulation through a communication strategy). Such guidance could clarify the meaning of “rely upon approval by a single IRB,” and clarify that relying institutions or their administrative offices, rather than relying IRBs, are expected to assess and ensure governance and legal compliance at the local site, working in cooperation with the reviewing IRB and institution and with a view towards harmonized procedures and practices. I recognize that federal regulatory agencies in the US lack have the power through command-and-control rules to prohibit institutions from conducting their own ethics review of research conducted by their employees and agents. By dint of constitutional design, it will be nigh impossible to enact a regulatory rule that mandates an ethics process equivalent to the UK. At best, regulation can be devised to further guide institutions as to the form and function of the sIRB rule and incentivize, be it through federal subsidies or nudges, a more centralized IRB review system.

Regarding the second weakness, elements of due process can be folded into a future regulatory rule that mandates a managed IRB appeals process for the sIRB. For example, the rule may provide applicants the option of appealing against the decision of the reviewing IRB and seeking a second opinion from another IRB at the same reviewing institution, or from an IRB at one of the relying institutions. The logistics of this managed process could be spelled out in OHRP guidance.

Even if further regulatory reform is possible to remedy of these weaknesses in the sIRB rule, there is no guarantee that the system will a success. Successful implementation will require both top-down and bottom-up systems in place. In the empirical research I conducted in 2015 and 2016 with international experts in research ethics oversight, it was evident that there must be a robust

overarching regulatory structure and committed leadership at the top that works to improve procedural consistency across all ethics committees participating in a “mutual recognition” ethics review system, be it through an sIRB model or another type.⁷² Some experts thought this top-down leadership was perhaps best addressed through statutory regulation (e.g. the EU Clinical Trials Directive 2001 and the UK’s Clinical Trials Regulation 2004) and other, “softer” forms of regulation (e.g. the UK’s GAFREC and REC SOPs) that work towards the same goals. In the US, it is doubtful that the currently existing relevant regulations, including HIPAA, are all aligned towards making the sIRB a success. These experts also stressed a concurrent need for a bottom-up, stakeholder-led initiative with committed buy-in to drive change in the regulatory approach; regulation alone, they stressed, cannot do the trick with committees of (non-ethics professional) volunteers scattered across institutions and jurisdictions. There is a need to build *trust* across all participating IRBs in cooperative research so that they can rely on both the ethics review and decision made by another. This will take time, and is likely more achievable when starting with smaller projects and then building up an evidence base and support, demonstrating the value of the system. Crucial mechanisms to help build this trust and buy-in are improved written and oral communication (i.e. both the frequency and platform of communication); harmonization of policies and procedures (e.g. a template ethics review form as with the UK’s NHS RECs; template reliance agreements; and harmonized SOPs); and operational planning that is in place from the beginning and sustained throughout (e.g. pilot testing; budget; administrative support; and interoperable infrastructures).

The lack of an effective top-down regulatory system can negatively affect procedural consistency and standards across IRBs, especially when coupled with the lack of a concerted, bottom-up, stakeholder-led effort to achieve consistency and mutual recognition between IRBs. The coupled absence can significantly undermine trust in and buy-in to a reformed regulatory system, which is what the sIRB signifies. Still, a top-down and bottom-up approach are feasible and worthwhile aspirations for the research ethics community in the US. Few will dispute that ethics review is essential for the maintenance of public trust and confidence in research. Many would agree that the traditional system of multi-IRB review for cooperative research was disproportionately burdensome, ineffective, and inefficient. The sIRB moves us towards a model of proportionate and efficient regulation. The remaining agenda of building and sustaining procedural and substantive harmonization across IRBs, as well as gathering an evidence base to assess whether the sIRB rule leads to improved efficiency of the review process while protecting and promoting the rights and interests of research participants, will require committed effort over the long haul. But there is inspiration to propel that effort, particularly if we look across the pond to the efforts being undertaken in the UK, Europe, and elsewhere.

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¹ Subpart A of 45 CFR 46. See DHHS, “Federal Policy for the Protection of Human Subjects,” 82 F.R. 7149, January 19, 2017 [hereinafter Common Rule – Final Rule], *available at* <https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects>.

² See generally Menikoff, J., “The Paradoxical Problem with Multiple-IRB Review,” *New England Journal of Medicine* 363, no. 17 (2010): 1591-1593; Schneider, C.E., *The Censor’s Hand: The Misregulation of Human-Subject Research* (Cambridge: MIT Press, 2015); Heimer, C.A. and Petty, J., “Bureaucratic Ethics: IRBs and the Legal Regulation of Human Subjects Research,” *Annual Review of Law and Social Science* 6 (2010): 601-626. See also McWilliams, R. et al., “Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study,” *Journal of the American Medical Association* 290, no. 3 (2003): 360-366; Abbott, L. and Grady, C., “A Systematic Review of the Empirical Literature Evaluating IRBs: What We Know and What We Still Need to Learn,” *Journal of Empirical Research on Human Research Ethics* 6, no. 1 (2001): 3-19.

³ Common Rule – Final Rule, *supra* note 1, at 7265.

⁴ Federally funded adult and pediatric cancer studies have had the option since 2001 of delegating review authority to the central IRB of the National Cancer Institute. Published research indicates it has had good success. See National Cancer Institute, Central Institutional Review Board for the National Cancer Institute, *available at* <<https://www.ncicirb.org/>>. See also Wagner, T.H. et al., “Costs and Benefits of the National Cancer Institute Central Institutional Review Board,” *Journal of Clinical Oncology* 28, no. 4 (2010): 662–666.

⁵ Townend, D. et al., “Streamlining Ethical Review of Data Intensive Research,” *BMJ* 354 (2016) 354: i4181.

⁶ Stark, L., “IRBs and the Problem of ‘Local Precedents’,” in Cohen, I.G., and Fernandez Lynch, H., eds., *Human Subjects Research Regulation: Perspectives on the Future* (Cambridge: MIT Press, 2014).

⁷ Common Rule – Final Rule, *supra* note 1, at 7154.

⁸ Dove, E.S. et al., “Ethics Review for International Data-Intensive Research,” *Science* 351, no. 6280 (2016): 1399-1400.

⁹ NIH, “Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research,” Notice No. NOT-OD-16-094 (June 21, 2016), *available at* <<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>>.

¹⁰ Uganda National Council for Science and Technology, “National Guidelines for Research involving Humans as Research Participants” (2014), s. 4.5.5, para. c.

¹¹ Dove, E.S. and Garattini C., “Expert Perspectives on Ethics Review of International Data-Intensive Research: Working towards Mutual Recognition,” *Research Ethics* 14 (2018): 1-25. See also Clinical Trials Ontario, *available at* <<http://www.ctontario.ca/>> and Ontario Cancer Research Ethics Board, *available at* <<https://ocreb.ca/>>.

¹² National Health and Medical Research Council, “National Approach to Single Ethical Review,” Australian Government (2018), *available at* <<https://www.nhmrc.gov.au/health-ethics/national-approach-single-ethical-review-multi-centre-research>>.

¹³ Rahimzadeh, V. and Knoppers, B.M., “How Mutually Recognizable is Mutual Recognition? An International Terminology Index of Research Ethics Review Policies in the USA, Canada, UK and Australia,” *Personalized Medicine* 13, no. 2 (2016): 101-105.

¹⁴ Lidz, C.W. et al., “Reliance Agreements and Single IRB review of Multisite Research: Concerns of IRB Members and Staff,” *AJOB Empirical Bioethics* 9, no. 3 (2018): 164-172.

¹⁵ Taylor, H.A., Ehrhardt, S. and Ervin A.-M., “Public Comments on the Proposed Common Rule Mandate for Single-IRB Review of Multisite Research” *Ethics & Human Research* 41, no. 1 (2019): 15-21.

¹⁶ DHHS, “Federal Policy for the Protection of Human Subjects,” 80 F.R. 53931 (September 8, 2015), *available at* <<https://www.federalregister.gov/documents/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects>>. DHHS initially proposed the sIRB rule in its Advance Notice of Proposed Rulemaking (76 F.R. 44512) in July 2011.

¹⁷ Common Rule – Final Rule, *supra* note 1, at 7208.

¹⁸ Klitzman, R. et al., “Local Knowledge and Single IRBs for Multisite Studies: Challenges and Solutions,” *Ethics & Human Research* 41, no. 1 (2019): 22-31.

¹⁹ Common Rule – Final Rule, *supra* note 1, at 7149.

²⁰ *Id.* at 7151.

²¹ *Id.* at 7150.

²² *Id.*

²³ The UK also has a hybrid, and one might say uncoordinated, system of RECs. Several different types of RECs exist. They can be split into two main categories of non-NHS RECs (e.g. institution-based higher education RECs) and NHS RECs, the latter of which are primarily charged with reviewing health-related research.

²⁴ An exception to this rule is the requirement that all non-clinical trials research involving adults lacking capacity in Scotland be reviewed by a specific REC known as the Scotland A REC. See *Adults with Incapacity (Scotland) Act 2000*, s. 51 and *Adults with Incapacity (Ethics Committee) (Scotland) Regulations 2002*.

²⁵ *Care Act 2014*, s. 110(2) (emphasis added).

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- ²⁶ Care Act 2014, s. 112(1) (emphasis added).
- ²⁷ Health Research Authority, "Information for Potential Research Ethics Service Committee Members," available at <<https://www.hra.nhs.uk/documents/1025/standard-application-pack-rec-members.pdf>> (emphasis added).
- ²⁸ Chief Scientist Office, "Research Ethics Structure in Scotland," available at <<http://www.nhsresearchscotland.org.uk/services/research-ethics>> (emphasis added).
- ²⁹ Office for Research Ethics Committees Northern Ireland (ORECNI), "HSC REC A & HSC REC B Executive Summary Annual Report 2015-2016," available at <http://www.hscbusiness.hscni.net/images/HSC_REC_A_and_HSC_REC_B_Executive_Summary_Annual_Report_2015-2016.doc>.
- ³⁰ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [hereinafter Clinical Trials Directive].
- ³¹ The reason why the EU did not mandate a single ethics opinion across the entire EU for a multi-site, multi-country clinical trial is that it lacks competence to regulate in research ethics, which is seen as an exclusive competence of the Member States.
- ³² The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by the Medicines for Human Use (Clinical Trials) Amendment 2006, SI 2006/1928. The amended Regulations were intended to give domestic effect to the EU's Good Practice Directive (2005/28/EC).
- ³³ This is currently reflected in Health Research Authority, "Standard Operating Procedures for Research Ethics Committees," Version 7.3 (2018), s. 5.2, available at <<https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/>>.
- ³⁴ Alberti, K.G.M.M., "Local Research Ethics Committees: Time to Grab Several Bulls by the Horns," *BMJ* 311, no. 7006 (1995): 639-640; Jamrozik, K., "The Case for a New System for Oversight of Research on Human Subjects," *Journal of Medical Ethics* 26, no. 5 (2000): 334-339; Warlow, C., "Clinical Research Under the Cosh Again," *BMJ* 329, no. 7460 (2004): 241-242.
- ³⁵ Health Research Authority, "REC Directory," available at <<https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/>>.
- ³⁶ Rahimzadeh, V., Dove, E.S., and Knoppers, B.M., "The sIRB System: A Single Beacon of Progress in the Revised Common Rule?" *American Journal of Bioethics* 17, no. 7 (2017): 43-46, at 43-44.
- ³⁷ Common Rule – Final Rule, *supra* note 1, at 7234.
- ³⁸ Dove, E.S., *Regulatory Stewardship of Health Research: Navigating Participant Protection and Research Promotion* (Cheltenham: Edward Elgar, forthcoming).
- ³⁹ Klitzman et al., *supra* note 18.
- ⁴⁰ Common Rule – Final Rule, *supra* note 1, at 7208.
- ⁴¹ Common Rule – Final Rule, *supra* note 1, at 7208.
- ⁴² U.S. Congress, House Committee on Government Operations, Research and Technical Programs Subcommittee, *The Use of Social Research in Federal Domestic Programs: Part IV—Current Issues in the Administration of Federal Social Research* (90th Cong., 1st. sess., 1967), at 221.
- ⁴³ Department of Health, Education, and Welfare, "Institutional Review Boards: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research," *Federal Register* 43 (30 November 1978), at 56176-56178.
- ⁴⁴ Gladue, B.A., "Gender Identity Politics, Human Subjects Issues, and the 'Law of Unintended Consequences,'" *Archives of Sexual Behavior* 37, no. 3 (2008): 448-450, at 449.
- ⁴⁵ *Supra* note 43.
- ⁴⁶ Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans* (2016), available at <<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>>.
- ⁴⁷ World Health Organization (WHO), *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants*, available at <http://ec.europa.eu/research/participants/data/ref/fp7/89857/research-human-participants_en.pdf>.
- ⁴⁸ Schneider, *supra* note 2, at 78, 83.
- ⁴⁹ See e.g. Green, L.A. et al., "Impact of Institutional Review Board Practice Variation on Observational Health Services Research," *Health Services Research* 41, no. 1 (2006): 214-230.
- ⁵⁰ Trace, S. and Kolstoe, S., "Reviewing Code Consistency is Important, but Research Ethics Committees Must Also Make a Judgement on Scientific Justification, Methodological Approach and Competency of the Research

Team” *Journal of Medical Ethics* 44, no. 12 (2018): 874-875, at 874. See also Trace, S. and Kolstoe, S., “Measuring Inconsistency in Research Ethics Committee Review” *BMC Medical Ethics* 18 (2017): 65 (1-10).

⁵¹ *Id.*

⁵² Dove and Garattini, *supra* note 11.

⁵³ *Id.*

⁵⁴ Common Rule – Final Rule, *supra* note 1, at 7265.

⁵⁵ *Id.* at 7209.

⁵⁶ Equivalent guidance was published in Wales and Scotland: DGM 98/25 and MEL 97/8, respectively.

According to the original Governance Arrangements for NHS Research Ethics Committees (GAfREC), MRECs “undertake the review of the ethics of the research protocol, including the content of the patient information sheet and consent form. No further ethical review of these items shall be undertaken by other RECs (except in the process of a ‘second review’ [...]).” See Department of Health, “Governance Arrangements for NHS Research Ethics Committees (Department of Health, 2001), at para. 8.7. Locality issues undertaken by LRECs were “limited to”: “the suitability of the local researcher; the appropriateness of the local research environment and facilities; specific issues relating to the local community, including the need for provision of information in languages other than English.” *Id.* at para. 8.8.

⁵⁷ Department of Health, “Review of Ethics of Multi-centre Trials,” February 1995, CMO’s Consultative Group on Research Ethics, RE/95/1, NPA, as quoted in Hedgecoe, A., “Scandals, Ethics, and Regulatory Change in Biomedical Research,” *Science, Technology, & Human Values* 42, no. 4 (2017): 577-599, at 586.

⁵⁸ Al-Shahi, R., and Warlow, C., “Ethical Review of a Multicentre Study in Scotland: A Weighty Problem,” *Journal of the Royal College of Physicians of London* 33, no. 6 (1999): 549-552; Larcombe, I. and Mott M., “Multicentre Research Ethics Committees: Have They Helped?” *Journal of the Royal Society of Medicine* 92, no. 10 (1999): 500-501; Dunn, N., Arscott, A., and Mann, R., “Costs of Seeking Ethics Approval Before and After the Introduction of Multicentre Research Ethics Committees,” *Journal of the Royal Society of Medicine* 93, no. 10 (2000): 511-512.

⁵⁹ Collett, C., “Setting the Strategic Landscape for the HRA – Ethics Governance” (2013) (unpublished internal Health Research Authority paper provided to the author), at 4 (emphasis in original).

⁶⁰ Diamond, M.P. et al., “The Efficiency of Single Institutional Review Board Review in National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network–initiated Clinical Trials,” *Clinical Trials* 16, no. 1 (2019): 3-10.

⁶¹ Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. 104–191, 110 Stat. 1936.

⁶² Coleman, C., “Rationalizing Risk Assessment in Human Subject Research” (2004) 46 *Arizona Law Review* 1-51, at 17.

⁶³ Townend D. and Dove, E.S., “Approaching Ethics Review Equivalency Through Natural Justice and a ‘Sounding Board’ Model for Research Ethics Committees,” *Medicine and Law* 36, no. 1 (2017): 61-86, at 74.

⁶⁴ Schneider, *supra* note 2, at xxvii.

⁶⁵ Baldwin, R., Cave, M., and Lodge, M., *Understanding Regulation: Theory, Strategy, and Practice* (2nd edn., Oxford: OUP, 2012), at 29.

⁶⁶ Fernandez Lynch, H., “Opening Closed Doors: Promoting IRB Transparency,” *Journal of Law Medicine and Ethics* 46, no. 1 (2018): 145-158, at 155.

⁶⁷ *Id.* at 153.

⁶⁸ On this point, see also Global Alliance for Genomics and Health, “Ethics Review Recognition Policy,” (2017) available at <<https://www.ga4gh.org/wp-content/uploads/GA4GH-Ethics-Review-Recognition-Policy.pdf>>.

⁶⁹ Townend and Dove, *supra* note 52, at 77-78.

⁷⁰ Health Research Authority, “Standard Operating Procedures for Research Ethics Committees,” Version 7.3, (2018), at para. 8.1.

⁷¹ *Id.* at para. 8.5.

⁷² Dove and Garattini, *supra* note 11.