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Thinking Locally and Acting Centrally in Human Research Subjects Research Oversight:  
Assessing the Goals, Content, and Appropriateness of Local Context Review for Multisite  
Research

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## ABSTRACT

A leading concern about single IRB (sIRB) review for multisite studies, as is now required by federal policies, is whether and how sIRBs consider local context in their review. While several types of local context considerations have been proposed, there is not shared agreement among those charged with the ethics oversight of human subjects research as to the goals and content of local context review, nor the types of research studies for which sIRB review might be inappropriate. Through a scoping review of published scholarship, public comments, and federal guidance documents, we identified five assumed goals for local context review: protecting the rights and welfare of local participants; ensuring compliance with applicable laws and policies; assessing feasibility; promoting the quality of research; and promoting procedural justice. While a variety of content was proposed to be relevant, it largely grouped into four domains: population/participant-level characteristics; investigator and research team characteristics; institution-level characteristics; and state and local laws. Furthermore, proposed characteristics for exclusion from sIRB requirements reflected both protection- and efficiency-based concerns. These findings can inform ongoing efforts to assess the implications of policies mandating sIRB review, and when exceptions to those policies might be appropriate.

## KEYWORDS

multisite studies, single IRBs, local IRBs, Common Rule, research ethics, human subjects research

## INTRODUCTION

The use of a single institutional review board (sIRB) is now required for most federally funded multisite human subjects research in the United States (US). In 2014, the National Institutes of Health (NIH) published a proposed draft policy to require most domestic NIH-funded multisite research to use a single institutional review board (sIRB) of record; following public comment and revision, the final policy went into effect in January 2018.<sup>1</sup> Similar requirements were introduced by the US Department of Health and Human Services as part of the 2018 revised Common Rule governing research with human subjects.<sup>2</sup> These requirements were implemented in response to concern that review by individual institutional review boards (IRBs) for multisite studies was inefficient and burdensome, delaying the generation of socially valuable knowledge and increasing research costs, and doing so without any evident benefit to the ethical conduct of research.<sup>3</sup> Requiring sIRB review, it was argued, would improve research efficiency while maintaining safeguards for—and respect of—research participants.<sup>4</sup>

These twin goals—improving efficiency while maintaining protections—are widely embraced. Yet whether they are *actually* advanced by sIRB review remains unclear.<sup>5</sup> At the time the sIRB requirements were enacted, empirical evidence regarding the effects of sIRB review on research was limited.<sup>6</sup> While several efforts have since been undertaken to explore the impact of the new sIRB review requirements, they have largely focused on the efficiency and consistency of sIRB review. Evaluations of the new requirements are ongoing, but limited evidence suggests the true potential for sIRBs to reduce the time for IRB review and study approval.<sup>7</sup> However, the impact of sIRB review on protections for human research subjects and the ethical integrity of research remains unclear.

A key challenge for ensuring protection of human subjects using sIRB review is whether and how sIRBs can collect and incorporate knowledge of the local context in their review. While the term “local context” is not currently defined in federal policies and regulations governing the protection of human research subjects, obtaining information about locations where the proposed research is to be conducted is an established part of sIRB review for domestic as well as international research that uses a sIRB.<sup>8</sup> As explained by SMART IRB (a platform funded by the US NIH Clinical and Translational Science Awards Program to support the adoption of the sIRB requirements) in providing recommendations for the harmonization of local context review, it derives from stipulations in the Common Rule (and similar FDA regulations) that require IRBs to “be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice,” and to be sensitive to such issues as “community attitudes.”<sup>9</sup> Notably, concern about local context was *the* most common argument offered against sIRB review in public comments on the proposed changes to the Common Rule mandate for sIRB review.<sup>10</sup> Furthermore, several studies have documented that challenges related to local context review are among the most frequently reported concerns among those tasked with implementing sIRB review, and stakeholders report a wide range of what is considered local context among different IRBs.<sup>11</sup> Similar confusion exists within the normative literature, with multiple observers noting the absence of agreement on what “local context” should entail.<sup>12</sup> This variation in understandings of local context raises at least three concerns. The first is justice-based, in that protection for current and/or future research participants may be inappropriately disparate across sites participating in multisite research. The second is beneficence-based, in that issues related to protection of and respect for research participants might be missed by an sIRB, which might be

unfamiliar with particular features of the research site and/or the populations it serves that may raise distinct considerations relevant for assessing the risks and burdens presented by proposed research activities. For example, a clinical trial in which one or more arms is “usual care,” an inaccurate understanding of what constitutes standard care at a particular site or for a particular subpopulation could result in the sIRB not being able to discern that the proposed research risks are reasonable and/or that these risks are not being adequately minimized, among other concerns.<sup>13</sup> The third is a concern about social value, in that the processes imposed by some organizations for local context review may introduce unnecessary administrative burdens that delay the conduct of research and, in turn, delay the application of newly generated knowledge to improve health.<sup>14</sup>

While several types of local context considerations have been proposed, there is not shared agreement as to the goals and content of local context review, nor the types of research studies for which sIRB review might be inappropriate. For example, both the NIH policy and the revised Common Rule acknowledge the potential for permissible exemptions to the sIRB requirements. According to the Common Rule, multisite studies involving tribal populations are exempt from the sIRB requirements, as is research “for which any Federal department or agency...determines and documents that the use of a single IRB is not appropriate for the particular context.” (45 CFR part 46.111) According to NIH policy, “requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception.”<sup>15</sup> However, the criteria by which such determinations might be made have not yet been articulated.

Describing such understandings of local context review by sIRBs is a necessary precursor to assessing the impact of the sIRB policy. To support this end, we conducted a scoping review to identify: (a) the assumed goals of local context review; (b) the relevant domains of local context that should be considered by an sIRB; and (c) the specific characteristics of a study and/or its population influencing the (in)appropriateness of sIRB review.

## METHODS

In collaboration with an informationist who has expertise in the retrieval and management of interdisciplinary information to support health research, we designed a search of the peer-reviewed literature to identify literature related to local context review. The search included articles from Pubmed (59 articles), Web of Science (264 articles), and EMBASE (39 articles) for an initial total of 362 articles (Fig 1). These databases were selected to cover a broad scope of the medical and multidisciplinary research literature. Titles and abstracts were initially screened by one author (KT), and any questions about eligibility were reviewed by a second author (SRM). Selection criteria were deliberately broad to capture the full range of literature, and included empirical reports and normative/opinion/policy analyses. Forward and backward citation tracking (e.g., identifying articles that cite to or are cited by key articles) was used to identify additional articles not captured through the initial search, yielding an additional 14 articles.<sup>16</sup>

We developed a standardized extraction tool using COVIDENCE<sup>17</sup> to capture information on: article type, mentioned goals of local context review, domains of local context, study type for which local context review was more/less applicable, and expressed concerns about sIRBs. All articles selected for full-text review were reviewed by one reviewer (KT or SRM), but if there was any doubt in making this determination, it was discussed with one or more coauthors.

We supplemented our review of the scholarly literature through collection and review of materials from five additional sources: (1) an internet search of federal policy and guidance discussing either local context or single or centralized IRBs; (2) a convenience sample of publicly available local context review forms, such as those developed by academic institutions and SMART IRB; (3) public comments on the September 8, 2015 Proposed Rule for Federal Policy for the Protection of Human Subjects (e.g., Common Rule); (4) public comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (December 3, 2014-January 29, 2015); and (5) public comments on the September 28, 2022 Proposed Rule by the Food and Drug Administration (Docket: Institutional Review Boards; Cooperative Research).

## RESULTS

Of the 376 scholarly articles initially identified, 7 duplicates were removed, and 317 were excluded for lack of relevance (e.g., did not pertain to IRB review or focused on an IRB topic other than review of multisite studies). 52 full text articles were assessed, of which another 11 were excluded for lack of relevance, resulting in 41 articles included in our qualitative synthesis. We grouped the findings into three domains: goals of local context review; domains of local context (e.g., specific features of the study population, investigators, institution, and/or legal landscape); and study-specific features influencing the (in)appropriateness of sIRB review.

### Goals of Local Context Review

The goals of local context review were rarely explicitly stated. Nevertheless, we identified five assumed goals, inferred through either concerns expressed about the impacts resulting from the absence of local IRB review, or statements made regarding the value of review by a local IRB.

These include: protecting the rights and welfare of local participants; ensuring compliance with applicable laws and policies; assessing feasibility; promoting the quality of research; and promoting procedural justice. Each will be described in turn.

First, local context review can support *protecting the rights and welfare of local participants*.

This is largely inferred through comments related to concern about the loss of review by local IRBs under a centralized approach. For example, in expressing concern about the proposed FDA rule requiring sIRBs, one commenter emphasized local IRBs as being “the most effective model for ensuring [protection of] the rights and welfare of local research participants.”<sup>18</sup> Similarly, qualitative research with IRB experts in 2011 found that local review is viewed as a means by which to fulfill an institution’s “moral obligation” to protect “our own” (sic) subjects—an obligation that might be undermined by if delegated to a sIRB.<sup>19</sup> Examples from the literature that are consistent with this view include arguments that local context review enables: understanding the local cultural context (including social, ethnic, linguistic, and economic factors) and identifying local features that could affect research design; tailoring consent materials and processes to ensure prospective participants understand and appreciate their decisions regarding participation; ensuring safeguards for vulnerable participants including minimization of undue influence, and providing familiarity with individual investigators and relevant knowledge of institutional infrastructure.<sup>20</sup>

Second, local context review was described as important for *ensuring compliance with applicable laws or institutional policies*, and, relatedly, for promoting protection from the associated legal liability.<sup>21</sup> For example, in a commentary critiquing the review of multicenter studies by multiple IRBs, a former director of the Office of Human Research Protections



observed that some institutional reluctance to rely on an outside IRB reflects concern that, if the study was later found to have not been in compliance with regulations, it might result in reputational damage for the institution and/or legal liability—despite its employees not being responsible for any misdeeds.<sup>22</sup> While this goal seems primarily focused on protecting researchers and institutions, rather than research participants, at least one scholar has proposed that mitigating liability also indirectly promotes beneficence, “because preventing harm to participants is vital to managing legal risks.”<sup>23</sup>

Third, local context review was described as important for *assessing feasibility*, including evaluating whether local resources are capable of managing the local application of a multisite protocol, and the likelihood of meeting study accrual targets given characteristics of the site population and as well as the potential for competing trials that might affect participant recruitment.<sup>24</sup> For example, for a study targeting a specific population with a rare condition, a site might have multiple existing trials open that do not allow co-enrollment in other studies.

Fourth, local context review was described as *promoting the quality of research*. This goal derives from general arguments about the value of local review—arguments that predate the establishment of the original Common Rule. As described by Surgeon General William Stewart in 1967, “local groups will have a much closer rapport with their communities and a better understanding of the meanings 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.”<sup>25</sup> More recently (2016), local involvement in IRB review has been described as improving the review of research with Tribal Nations, supporting the creation of research measures that were “sensitive to cultural needs while maintaining scientific integrity.”<sup>26</sup>

Finally, another goal is grounded in *procedural justice*, based on the argument that local IRB review can involve the local community in decisions pertaining to the review of research, and that local IRBs “may be more accountable and accessible than central IRBs, because local IRB members live in the community and interact with community members on a daily basis.”<sup>27</sup> A related argument is that local context review can serve a *legitimizing function*, in that studies that have undergone local review may be perceived by participants and the broader public as better addressing local sensitivities.

#### Domains of Local Context Review

We identified four domains of local context described as relevant for local context review: population/participant-level characteristics; investigator and research team characteristics; institution-level characteristics; and state and local laws.

*Population/participant-level characteristics* included those pertaining to: (a) demographic characteristics, including race/ethnicity, religious affiliations, socioeconomic status, and educational attainment; (b) culture and religion, including relevant dietary or other restrictions relevant to research interventions, stigma associated with the conditions/behaviors/populations under study, gender roles, and privacy; (c) language and literacy; (d) geography; (e) community attitudes towards research; (f) vulnerable populations, including specific considerations for recruitment and retention, safeguards for rights and welfare, and availability of relevant social services; and (g) appropriateness of incentives. For example, in a recent empirical study exploring implementation of an sIRB, an IRB director offered the example of a medication study

that required participants to consume a specific high-fat diet to facilitate drug absorption, and therefore excluded fish from the list of permitted foods for consumption—an exclusion that the director suggested could cause particular adherence challenges for members of their local population, which included a large percentage of Catholics who refrained from eating meat on Fridays.<sup>28</sup>

*Investigator and research team characteristics* included: (a) competency/training, including experience with the relevant clinical and research activities and training in the responsible conduct of research and research ethics; (b) credentialing for study team members, including for particular study-related procedures, and whether members were in good standing with licensing boards and other regulatory authorities; (c) conflicts of interest; (d) history of compliance issues or prior disciplinary actions; (e) prior experience with multisite research studies; and (f) the number of other current protocols being managed by investigators. These considerations were described as relevant for assessing whether a research team at the local institution could feasibly conduct a study, and the likelihood that the research would be conducted with appropriate scientific and ethical standards, given the study team members' prior research conduct.<sup>29</sup>

*Institution-level characteristics* included: (a) local standards of care; (b) recruitment considerations, including potentially competing studies and the availability of sufficient potential participants; (c) institutional policies, including those related to contraception, compensation for injury, and recruitment of patients, employees, or other vulnerable populations; and (d) site-level resources and capabilities, including space, equipment, drug and device storage, handling and dispensing practices, data storage capacities, and personnel. Specific resources and capabilities included those pertaining to radiation and institutional biosafety, as well as financial

considerations such as research billing and Medicare qualifying review. These considerations were described as relevant both for assessing the feasibility and safety of the research within the local setting, and for disclosure of information within consent forms. For example, religiously affiliated hospitals may be precluded from including reference to specific contraceptive practices.<sup>30</sup>

*State and local laws* related to research included those pertaining to: (a) age and decision-making, including age of majority, age of assent, mature/emancipated minors, adults with impaired decision-making and impact on legally authorized representatives, wards of the state, and other laws related to informed consent; (b) confidentiality, including data security and privacy notification requirements; (c) public health, including mandatory reporting and communicable disease disclosure; (d) restrictive laws, including for drug use, abortion, or sexual behavior; and (e) sovereign immunity for state institutions.

#### Study-Specific Features Influencing the Appropriateness of Single IRB Review

In public comments on proposed revisions to the Common Rule to require sIRB review and on related policy proposals by the NIH and FDA, several commentators expressed concern about the breadth of the sIRB requirements, suggesting the need for a more flexible approach that reflects the different considerations posed by different types of multisite research activities.<sup>31</sup>

A wide range of participant- and study-specific features have been proposed as relevant for assessing the appropriateness of sIRB review. These features reflect concerns related to the two goals of sIRB review, namely, the protection of research participants and the efficiency of ethical review.

We identified at least three types of protection-based concerns regarding the potential (in)appropriateness of sIRB review for certain studies. The first—currently included as an exemption from both the NIH and Common Rule requirements for sIRBs—relates to studies involving tribal populations, and the importance of ensuring appropriate consideration of the relevant political, social, cultural, and spiritual considerations during IRB review.

The second type relates to studies involving *innovative, high-risk research*,<sup>32</sup> and the associated risks for both individual safety and institutional liability, as well as the related importance of rapid communication of new findings that may impact participant safety. Relevant examples include trials involving stem cells or gene therapy, first-in-human studies, and Phase I/II studies in which the safety profile is being assessed. As one commenter on the proposed NIH policy explained, “first in human research protocols involve many issues regarding dosing changes and require a close working relationship with [the] research pharmacy.”<sup>33</sup> Further, Phase I studies often involve “dose changes, changes in cohorts, and increases in subject population” requiring IRB review, along with “management of protocol violations, deviations and eligibility exceptions”—issues that were anticipated to be “very difficult to manage” when the requests have to go to an outside IRB, and thus were viewed as likely to increase, rather than streamline, the time for review.<sup>34</sup> Related concerns have been raised about surgical studies, based on the rationale that the risks in surgical settings are more dependent upon the skills of local surgeons and the resources and processes of the local hospital, as compared to those in other study contexts.<sup>35</sup>

The third relates to studies involving *political, controversial, or sensitive issues*,<sup>36</sup> and related research for which sIRB review may be “unable to meet the needs of specific populations.”

Relevant examples include research involving: (a) unique ethnic or religious groups;<sup>37</sup> (b) potentially stigmatizing conditions;<sup>38</sup> (c) prisoners, given local and state-level variability in access to and permissions for this population;<sup>39</sup> (d) marginalized groups;<sup>40</sup> and (e) groups that have a historically contentious relationships with IRBs or with research.<sup>41</sup>

A separate line of study-specific concerns relate to efficiency. Specific examples suggested in which sIRB review may not improve efficiency include: studies with a limited number of sites (e.g., fewer than 5);<sup>42</sup> minimal risk studies, research studies that are not clinical trials, or studies eligible for expedited review;<sup>43</sup> and non-clinical studies for which the sites are not conducting the same research activities, such as social science studies for which each site may be conducting discrete portions of the research.<sup>44</sup>

Finally, some concerns relate to both protection and efficiency. For example, as described by an academic institution in response to the NPRM for the Revised Common Rule,<sup>45</sup> studies involving researchers or research groups at specific sites with a history of compliance issues may require more frequent review in the interest of protecting research participants. Under an sIRB, this would require either modification of the review cycle for all sites, or different review cycles by site—either of which could impede, rather than promote, research efficiency. Related concerns have been raised about the inappropriateness of sIRB review for studies operating under an Exception from Informed Consent (EFIC) for emergency clinical research,<sup>46</sup> due to the potential that these studies may create controversy within a local community, and that federal rules require researchers to consult with members of the community in which the study will be conducted.<sup>47</sup>

Finally, a range of concerns have been raised related to studies involving epidemiological, public health, or social science research.<sup>48</sup> For example, in a public comment on the proposed NIH

policy, the steering committee of the Study of Women's Health Across the Nation, a multi-site longitudinal observational cohort study of mid-life aging and menopause, described how the distinct population of racial and ethnic groups across each of the study's seven sites required different recruitment and retention strategies—differences that, according to the commenter, would present substantial challenges for an sIRB to review so as to adequately consider the different needs of the different populations.<sup>49</sup> Furthermore, site-specific studies meant there were “various combinations of protocols among the 7 sites,” creating a diversity in reviewing needs that might undercut the desired efficiency gains.<sup>50</sup>

## DISCUSSION

This scoping review presents the first attempt at a comprehensive account of the goals of local context review and the domains of local context that should be considered as part of that review, along with an exploration of the types of studies for which exceptions to requirements for using an sIRB might be appropriate. Our findings suggest at least four insights for future scholarship and policy.

First, while the lack of de facto local context review has been widely cited as an argument against sIRBs, the purpose of this review is often unspecified. This lack of clarity and consensus on the goals of local context review may be one explanation for disagreements about its relative importance to ensure appropriate protections for participants within a sIRB review model.<sup>51</sup>

Insufficient clarity or agreement about these goals may also contribute to current variation across sIRBs in the content, timing, and assessment of the information collected as part of local context review.<sup>52</sup> Future work should explore these disagreements, and the extent to which the domains currently included in assessments of local context align with the desired goals of local context review. Ultimately, the results of such work could be used to develop, articulate, and disseminate

clear expectations for local context review, and to facilitate the adoption of local context review by sIRBs.

Second, the considerations proposed as relevant for assessing the local context are both extensive and varied. Obtaining sufficient input from local sites on every consideration identified as potentially relevant for assessing local context requires considerable effort and time—investments that, as others have noted, may challenge the hoped-for improvements in efficiency promised by the sIRB model.<sup>53</sup> Future work might explore the types of information that are necessary for local context review, the relevance of collecting certain types of information by study type, and the relative priority of certain types of information, which might serve as screening mechanisms for IRBs to quickly identify any potential issues that would be considered “deal breakers” within their respective settings.

Third, little if any empirical evidence exists to inform whether the domains of local context review identified as relevant advance the purported goals of this review. Future work is needed to assess the relationship between the information currently collected as part of local context review and the impact on ensuring the protection of human subjects within a sIRB model.

Fourth, while the NIH policy states that exceptions to the sIRB requirements will be considered if there is a “compelling justification” for the exception, there remains uncertainty over when and for what purposes the NIH might grant such exceptions. Similar uncertainty exists related to permissible exceptions under the Common Rule. In a public comment to the proposed NIH policy, Public Responsibility in Medicine and Research (PRIM&R) called upon the NIH to convene an expert panel to develop criteria by which to assess the appropriateness of sIRB review for different research approaches.<sup>54</sup> Our findings of both protection- and efficiency-based



arguments suggest potential criteria to support this end. However, further work is needed to vet these criteria with key stakeholders.

## CONCLUSION

While concern over the loss of local context has been a leading argument against an sIRB review, the purpose of local context review, and what it should entail, remains underspecified. The absence of a shared understanding of what local context review is meant to achieve, and the considerations it should address, impedes understanding of the implications of policies mandating sIRB review—and when exceptions to these policies might be appropriate. This review presents a first step towards that end. Future work should engage key stakeholders responsible for the design, conduct, and ethical oversight of multicenter studies governed by sIRBs in this work.

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