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Adrift in the Gray Zone: IRB Perspectives on Research in the Learning Health System

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Abstract

Background—Human subjects protection in healthcare contexts rests on the premise that a principled boundary distinguishes clinical research and clinical practice. However, growing use of evidence-based clinical practices by health systems makes it increasingly difficult to disentangle research from a wide range of clinical activities that are sometimes called "research on medical practice" (ROMP), including quality improvement activities and comparative effectiveness research. The recent growth of ROMP activities has created an ethical and regulatory gray zone with significant implications for the oversight of human subjects research.

Methods—We conducted six semi-structured, open-ended focus group discussions with IRB members to understand their experiences and perspectives on ethical oversight of ROMP, including randomization of patients to standard treatments.

Results—Our study revealed that IRB members are unclear or divided on the central questions at stake in the current policy debate over ethical oversight of ROMP: IRB members struggle to make a clear distinction between clinical research and medical practice improvement, lack consensus on when ROMP requires IRB review and oversight, and are uncertain about what constitutes incremental risk when patients are randomized to different treatments, any of which may be offered in usual care. They characterized the central challenge as a balancing act, between, on the one hand, making information fully transparent to patients and providing adequate oversight, and on the other hand, avoiding a chilling effect on the research process or harming the physician-patient relationship.

Conclusions—Evidence-based guidance that supports IRB members in providing adequate and effective oversight of ROMP without impeding the research process or harming the physician-patient relationship is necessary to realize the full benefits of the learning health system.

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Background

Between clinical trials of new drugs and devices and decisions about which among existing interventions constitutes the best treatment for a patient or best practice for a hospital lies a complex and vexing gray zone for human subjects protection. The tools of clinical research —carefully controlled comparison, randomization, control of bias, evidence gathering—not only answer basic scientific questions, but can be used to make medical practice within and across institutions better: more efficient, safer, and more effective. Research on medical practices (ROMP) offers a systematic approach towards "continuous improvement and innovation, with best practices seamlessly embedded in the care process, patients and families active participants in all elements, and new knowledge captured as an integral by-product of the care experience" (IOM 2012:136). This articulation of the 'learning health system' raises difficult questions about appropriate ethical oversight: 1) What approach to ethical oversight and consent ought to be required to protect patient participants and with whom do the responsibilities lie when we rely on the tools of research within usual, day-to-day care, as we do in comparative effectiveness research and quality improvement studies? 2) And how should those charged with oversight assess risk in this context?

Guidelines that address these highly debated questions in clinical research have already been developed and codified in human subjects regulations and policies around the world. In the U.S., clinical research usually requires ethical oversight from an Institutional Review Board (IRB) (45 CFR 46, Subpart A). However, because ROMP is often conducted in the context of healthcare delivery and typically compares approved treatments that are all accepted within usual medical practice, it presents unique challenges to established IRB practices for assessing experimental or unproven treatments.

Existing human subjects protections often assume a principled distinction between research activities and clinical practice, even while acknowledging blurred lines in practice. In the Belmont Report, the National Commission for the Protection of Human Subjects acknowledged that "the distinction between research and practice is blurred partly because both often occur together" but went on to define practice as "interventions that are designed solely to enhance the well-being of an individual patient... and that have a reasonable expectation of success" and research as activities designed to "develop or contribute to generalizable knowledge" (Belmont 1979). However, the acknowledgment of blurred lines was not adopted in federal regulations, which maintained a principled line between these activities[1] (45CFR46). Identifying these boundaries has become especially challenging in the learning health system as these domains and aims are necessarily intertwined. For example, the potential benefits of ROMP are intended to extend well beyond the individual patient and yet research activities, such as evidence gathered for controlled comparisons of outcomes, may be difficult to distinguish from the usual care that a patient would receive. This ambiguity makes it difficult to determine whether and how these activities ought to be

[1]Although the Belmont Report does not specifically recognize the blurred lines between quality improvement and research activities, it does recognize a gray zone for addressing innovation. It notes that when physicians depart "in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research." This blurring of research and practice in the form of innovative treatment was not codified in regulation. The gray area resulting from innovation is largely, though not entirely, outside the scope of this paper.

reviewed. A key challenge will be to more clearly characterize the incremental or added risk of methods for ROMP such as retrospective chart review or prospective randomization of approved therapies (IOM 2007, 2012; Faden et al. 2013; Kass et al. 2012; Largent et al. 2011; Casarett et al. 2000).

On October 24, 2014, the Federal Office for Human Research Protections (OHRP) issued the draft guidance "Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care" to support IRB members in assessing the risks of comparative-effectiveness research. The guidance stipulated that the risks of any treatments included in this type of research should be disclosed to patients as research related risks, even if patients would normally receive one of these treatments without participating in the specific study. The guidance raised immediate questions about whether a standard of "reasonably foreseeable risk" was appropriate and if so, what it might imply for disclosure to patients, consent, and the feasibility of ROMP. However, to date, little empirical work has informed this important debate and the potentially far-reaching implications of this policy on patients, physicians, researchers, and IRB members.

To address this gap, we present qualitative data from focus groups of IRB members from three academic medical centers. The qualitative findings from these focus groups help characterize the ethical and regulatory "gray zone" between clinical research and the range of activities aimed at improving medical practice, illustrating the challenges facing IRBs and the central empirical questions in need of further investigation.

Methods

This qualitative study was designed to inform the development of a national survey on IRB members' and patient perspectives on ROMP. (Cho et al. 2015). We conducted six semi-structured, open-ended focus groups between January 2014 and March 2014 at three academic medical centers. In addition to its usefulness for hypothesis generation (Krueger 1994) and for supporting the development of survey items (Wolff et al. 1993), focus group methodology was chosen due to its suitability for exploring perspectives and attitudes when little empirical work is available on a particular research question (Stewart et al. 2007) as well as for hypothesis generation (Ryan and Bernard 2003; Corbin and Strauss 2007). IRB approval was obtained at Stanford University and Seattle Children's Research Institute.

Focus Group Recruitment and Facilitation

We conducted six focus groups with IRB members, recruiting a total of 22 IRB members across three institutions. Participants included health professionals and community members who had served on an IRB for an average of 7 years, with a range of one to 30 years. Members of the IRB were contacted by email.

The study guides were developed based on a review of the existing literature and an iterative discussion among all study investigators. Draft guides were piloted at each site and revised accordingly (Appendix A). Different means of conducting ROMP were introduced in the focus groups and participants were asked to share their perspectives on ethical issues including the definition and oversight of ROMP, randomization within standard care, risks

associated with randomization, and approaches to informed consent and disclosure of information. A senior research team member (SSL, MK, MC, BW) moderated each focus group and at least one additional team member was present for observation and note-taking (SAK, CJ, EB). Facilitators at all sites used the same semi-structured focus group guide. Focus group discussion was audiotaped. Immediately following each focus group, the facilitator and observer(s) met to debrief on the session.

Data Analysis

Audio recordings of the focus groups were transcribed and the transcriptions were verified by the study team members who had served as observers/note takers for each session. All data were uploaded to the qualitative data analysis software Dedoose. Initial codes included a combination of deductive codes from the literature, some deductive codes from the focus group guide, and codes generated inductively through collaborative reading and analysis of a subset of transcripts. The combined code book was then finalized through successive iterations into categories and codes. The full study team reviewed the final codebook. Each transcript was coded independently by primary coders (SAK, CJ) and secondary coders (MK, SSL), who reviewed and revised the initial application of codes. We relied upon modified grounded theory to analyze our data and used a combination of *a priori* coding derived from key concepts in the existing literature and *in vivo* substantive coding based on concepts and ideas that emerged from the focus group discussion. This approach is particularly well suited for exploratory research of this nature and our goal of hypothesis generation (Ryan and Bernard 2003; Corbin and Strauss 2007).

Results

Our focus groups revealed that IRB members are struggling to more clearly define and evaluate this newly expanding domain of research. This struggle characterizes the “gray zone” between clinical research and research within learning health systems. We identified four major themes that were present across the focus groups: 1) the blurred line between research and clinical care, 2) the challenges of identifying when activities require IRB review and oversight, 3) the challenges of identifying and evaluating incremental risks associated with research approaches such as randomization of patients to clinical care, and 4) attitudes about what constitutes appropriate consent and disclosure of ROMP to patients.

1. At the Heart of the Gray Zone: Is ROMP research and what makes it so?

Many IRB members in our study were uncertain about whether to characterize certain ROMP activities as research. As IRB members, they recognized the existence of regulatory distinctions between clinical research and quality improvement, but when pressed to articulate these, felt that the differences were not always clear in practice. Most participants struggled to define the boundary between research and quality improvement (QI), or comparative effectiveness research (CER), thereby indicating a “gray zone” where activities do not fit neatly into one or the other category.

> There are gray zones on both sides, and on one end would be ... where does quality assurance/quality improvement end and research begin? And on the other end would be when you're looking at innovative new things that no one has ever done

> before, which clearly is in the sort of novel innovation rather than practice research methodology, so I would see it sort of as defining the middle zone of what we're trying to talk about. (FG #3)

Citing the shift to learning health systems and the use of new technologies in data collection and analysis, some IRB members expressed confusion when trying to identify when activities constituted research within usual medical practice versus QI or CER.

> Because we're getting to these learning healthcare systems where every patient is generating data that somebody's looking at with computers, and they're going to draw conclusions from. So, in a way that's research, but it's also directed to the patient. It blurs the classic Belmont Report, nice and clear: 'this is research that isn't'... I don't see that that's the case anymore. (FG #1)

Some IRB members worried that lack of clarity might result in some activities being mis-identified as QI, or even deliberately described as QI to avoid lengthy IRB review. They were concerned that without thorough evaluation by an IRB, a full assessment of risks and benefits to patients or assurance of informed consent would not be achieved.

> One of the main things that the IRB does is look at the risk/benefit for the subjects, and we spend a lot of time talking about how to present that in the consent form... [P]resumably none of that happens in a QI type thing where somebody's asking 'Is there a risk to the subjects?' I mean presumably there isn't, but I would argue that ... it's supposed to be one of our main goals ...to understand the risks/benefits and make sure that the subjects are adequately informed about that risk/benefit, and whether or not that happens in a QI situation, I don't know. (FG #2)

> I think that's the process that all of us go through when we're trying to determine 'Is it human subjects? Is it QI?' and I think you're right. I think it's a muddy question... that sometimes is a good excuse, unfortunately. (FG #2)

IRB members appreciated the need for research on medical practice to improve care and also recognized that a shift toward learning health systems is already widespread. Yet, IRB members expressed concern that patients may fail to appreciate the underlying rationale for conducting research within medical practice. This potential disconnect underscored what many IRB members felt was the need for patient education on ROMP and the learning health system. We have discussed this further in another publication from our study of patient perspectives (Kelley et al. 2015).

2. Uncertainty and Disagreement about IRBs' Obligation to Review ROMP

Given IRB members' uncertainty about whether ROMP constitutes human subjects research in the clear sense assumed by current regulations, it is not surprising we observed disagreement about whether IRBs should be reviewing ROMP.

> The real question is what needs to be reviewed and who needs to review it. If you can't separate research from practice, are we going to review everybody's practice? That's starting to come, I think, with computerized care. People are looking at which drug did you use and did that work and did you do the right thing. I think

> medicine's coming under increased scrutiny. It's clinical care—forget whether you call it research or not. (FG #1)

IRB members wrestled out loud with this question and tried to identify certain factors that might tip activities from quality improvement to research. As a baseline, most IRB members emphasized that, "just collecting the data is not research" (FG #1). Beyond this, they suggested IRB review might be warranted if proposed activities identified a specific research question, or if there is intent to publish, to change practice, or to examine specific clinical endpoints for a group of patients. There was not clear consensus on this list—for example, some participants noted that publishing case studies did not constitute research—but the common suggestion was to try to identify the intent of the activity as aiming toward generalizable information.

> Our job is to determine 'actually, you know, this isn't research,' and we think about it in terms of the definitions of generalizable knowledge, like 'Are you just trying to figure out what's going on in your hospital, in your group, or are you actually trying to publish something, change guidelines?' that sort of thing. (FG #2)

Requiring patients to engage in procedures, such as blood draws or clinical visits that go beyond what would be expected in the course of usual care would also tip the balance toward an activity being research.

> Are there additional things that we would be asking patients to do, additional assessments, things that could introduce risk, you know additional blood tests or visits or procedures? (FG #2)

Reflecting on scenarios presented in the focus groups that described randomization of patients to two drugs for treating hypertension, some IRB members felt that the systematic investigation of patient outcomes put randomization activities into the category of research.

> The last two, the cluster and the point of care, start to ooze into research, which requires more formalization [formal review] because they're going to be randomized. (FG #1)

> I mean I know all the drugs are FDA approved and supposedly there's equipoise amongst the drugs, and that they're not changing practice of treating the hypertension with an antihypertensive. They're still treating adequately and to the best of their clinical practice, but I think when it says that 'they're now agreeing to randomize patients', now...it is no longer just standard of care. (FG #2)

There was more uncertainty among IRB members on whether randomization of patients to clinical approaches offered routinely in usual care clearly fell into the category of research. A critical point for IRB members was the information conveyed to patients about assignment to treatment approaches, including its rationale and the ability of physicians to change course.

> And what are the patients told about the ability to change drugs? 'If this isn't doing it for you, then we're going...what is our treatment plan? It's not just to give you drug A. You're going to start out with drug A and let's see how it goes, and if that doesn't work, then we'll try something else.' If any of these [studies] lock them into

> a system where they can't change, then I don't know if that's research or just bad practice. (FG #1)

The focus groups revealed no consensus on what guidelines should determine when IRBs should review ROMP. Although IRB members tended to associate certain features with research, such as organized efforts to generate and analyze treatment data and the intent to apply results in clinical practice, disagreement was more evident regarding how to categorize investigations involving randomization. As mentioned in the previous section, some participants were very concerned that QI or CER might not be reviewed for risks and benefits to patients, but others thought this fell outside the scope of traditional human subjects oversight.

3. Challenges in Identifying Incremental Risks of Randomization

One of the main issues at stake in thinking about appropriate oversight for ROMP is what constitutes incremental risk above and beyond the risks of routine clinical practice. When probed about different research approaches, from retrospective chart reviews to randomized cohorts or clinics, IRB members identified different levels of risks for various designs and distinguished retrospective from prospective studies. They expressed less concern about potential risks from retrospective review of medical charts because it does not involving deviating from the care that patients would normally receive.

> From the perspective of the participants in this kind of a study, they're really not participants at the time they're getting treated, they're just going to their doctor, they're just getting standard ... whatever the doctor says, and then sometime later somebody's going to go back and look at it, so they don't feel like they were part of a research study at the time. They were just given treatment from their doctor, and then somebody decided to go back and look and see what their outcomes were.

When asked about randomized approaches to ROMP, IRB members suggested that prospective studies involving randomization were also difficult to distinguish from what would otherwise occur when variation exists in the treatment routinely recommended by physicians. IRB members struggled to identify additional risks from randomization beyond the trial and error or arbitrariness of usual care, or found the risks to be negligible.

> I think in most cases, randomization in a well-defined study adds no incremental risk. (FG #3)

> Now your personal preference as a patient may be, oh my god, I hate medicine. I really want surgery or vice versa. You get to make that decision, but the risk, the moving it from who's got the next available clinic slot to see you to I flip a coin to get a better statistical view of the data? I think that adds no risk. (FG #3)

IRB members noted that this perspective assumes that the treatment options to which patients were randomized were comparable. However, some IRB members suggested that the rationale for randomizing patients to treatments is based on the working hypothesis that there may be important differences in patient outcomes. They struggled with how to address these as potential risks to any individual patient in the study.

> [Y]ou're assuming that there's equipoise, when in fact there isn't any data showing that probably these drugs have never been compared next to each other. I think the ethics of all this depends on the absolute certainty that you don't know that one of these is better - that you have true equipoise. (FG #1)

Underlining their belief that studies involving randomization should be reviewed by the IRB, some IRB members expressed particular concern about the impact of cluster randomization on patient autonomy, citing greater barriers to patients' ability to exit a study.

> The cluster randomization is the one that I actually have the most ethical concern about because ... can you actually as a patient opt out and go to another facility if you don't like whatever option is being randomized? At least with point of care, you can tell your doctor, I would hope with informed consent and everything, 'I don't want to be part of this study'. (FG #2)

Possible Risk of Receiving a Less Effective Treatment as a Research Participant—IRB members considered the uncertain efficacy of an assigned treatment as a potential risk of studies involving randomization worth disclosing to patients. This judgment was made on the grounds that patients who had not been enrolled in research might have received an alternative drug that resulted in better outcomes.

> You're ... exposing them to a risk as a consequence of participating in a study that compares treatment regimens where one may be riskier than another or one may be more effective than another. (FG #3)

Noting that study results would accumulate over time and relative risks associated with various clinical approaches would become known, IRB members thought one challenge for reviewers and for the consent process would be to anticipate risks of usual care that might be revealed in the future by virtue of more careful study, but are unforeseen at the time of consent.

> [I]f it turns out that after you've done the study you determine that one was more effective, then all of the people who were randomly going to the doctor that was giving the inferior treatment were at more risk, but they didn't know it, and the ones who were going to the doctor that was giving the superior treatment were at less risk and they didn't know it. But if you put them together in a randomized study, then it all of a sudden is presented right in front of them and they're asked to accept the risks that before they never would have even thought about, so the perception is quite different. (FG #3)

This participant's observation reflected how IRB members responded to the question of incremental risk by noting that ROMP can make risks of usual care real for patients in a way that might not ordinarily occur. By virtue of being carefully observed, studied, and documented, these risks are brought into the light for patients who otherwise might not have considered them.

Randomization Might Harm the Physician-Patient Relationship—Many IRB members raised concerns over how randomization would impact the clinical relationship. They underscored the importance of trust that patients place in their physicians' clinical

decision-making and worried that randomization, insofar as it might remove clinician control over patient care, could undermine patient trust.

Some IRB members expressed concerns that randomization might create risk for the physician-patient relationship if it were implemented in a way that deprived patients of information about their clinical choices.

> This is also a conversation about the provider and not about the patient, and you know if it's not randomized, then they get to get information from their provider and they get to have a discussion and make a decision with their provider, whereas if the provider is making a decision to randomize and the patient doesn't know about it, then they're not involved in that process anymore. (FG #2)

> I think if it involves a change in behavior from what a given patient would normally have undergone or what the relationship with the clinician was going to be, then that automatically raises the ethical bar in terms of transparency when the patient communicates with their doctor on 'How are you reaching this decision? Do I even have a choice in the decision? (FG #2)

Although IRB members struggled with how to characterize the added risks of randomization, they underscored the importance of transparency and of maintaining trust between physicians and patients as one way of mitigating these risks.

4. Lack of Consensus on Consent

Identifying the best approach to consent and disclosure and what information is important to relay to patients, particularly with respect to risk, pose challenges for assessing ROMP. The focus groups of IRB members did not produce a unified position on these issues; rather, participants tended to emphasize the need for flexibility and creativity in best protecting the interests of patients.

Agreement on Transparency, Disagreement about Individual Consent vs. Notification—Most IRB members felt that transparency about research on medical practice to patients was important and, in particular, that studies involving randomization should be fully disclosed to patients even if they do not include a formal consent process.

> I think if we're going to randomize a patient, [whether with] consent, [or] not consent...I think full disclosure to the patient should be the priority. Full disclosure. (FG #2)

On the whole, IRB members thought most patients would want to know about any deviation from usual care, particularly if it impacts their physician's clinical decision-making.

> Well, I think part of the ethical difference is exactly what you said, that the patient's perception is a very different thing. If they're relying on their doctor to make the choice in their best interest and they believe that the doctor is going to be able to make a wise choice then they would want to be informed and have the opportunity to consent or not to consent if something was going to happen. Even though from our perspective it may be completely meaningless, from their perspective it is not. (FG #3)

Other IRB members asserted that all prospective studies, including those involving randomization, require patient consent.

> Presumably, if there's going to be any randomized approaches where it's actually prospective studies ... then patients would participate in the study and would be consented. (FG #1)

However, IRB members disagreed on whether consent from patients, as opposed to notification, should be required, suggesting that as long as there was full disclosure, asking patients for their permission would not be necessary.

> I wasn't talking about informed consent. I'm just talking about a personal conversation with your patient and saying, 'Here's what we're doing in this institution. We're randomizing and that's what we've been doing,' and if the patient says 'Well I need more information on the drugs,' then you have to give more information on the drugs. (FG #2)

> But if we're back to the original randomization where patients are actually randomized to get different drugs, individually or by a site, I keep going back and forth. I just don't think there's any additional risk to the patients and so if there's no additional risk then just notification that their doctor or their institution is in a study doesn't increase the risk for them to participate, so what are they consenting to exactly? (FG #1)

Disagreement About Which Risks Should Be Disclosed—In discussing what information should be included in the consent forms, IRB members returned to the difficulty of how to characterize added risk from the research activities. Many IRB members focused on the question of what added risk is created by randomization for patients beyond the risks from the disease for which they were being treated. Some IRB members emphasized that incremental risk from research may vary as a function of underlying clinical risks.

> I think people should be informed of the risk of being involved in the trial, and sometimes that's—you're in an extraordinarily high risk clinical situation and the incremental risk of the study is essentially none, or you could be in a low risk clinical situation where the risks are unknown. (FG #3)

Other members challenged the need to disclose risks that would already be incurred as part of usual care.

> I think it comes also to the same questions of: should they disclose standard of care risks? And I agree that I don't think they should, but usually if you're going to have procedures, you have a separate consent form for your surgical procedure that you sign and that gives you the risks for that. If you get drugs prescribed, you get the whole pamphlet with your drug that describes the risks and all of that is in the standard of care. So, I don't think that should be included in the consent form when you're looking at research of medical practice especially. I mean it happens all the time on research consent forms that they include those, as I said earlier, and I don't think they should be there then either because it confuses the issues. (FG #1)

Tradeoff between Transparency and Too Much Information—Overall, IRB members recognized the importance of transparency in ROMP but underscored the challenging trade-off between transparency and overwhelming patients with too much information. They thought one confounding factor in striking this balance in ROMP might be that patients are often not well informed about the risks of clinical care as compared to what is expected in risk disclosure in research settings.

> You bring up an excellent point that the ethicists are beating us up [about]...you say here, I'm giving you a 48-page consent form that you're using regimen A and regimen B and they're essentially identical except this one little wobble in the middle... And you say, well, we don't tell them that clinically, and they say you should. So, part of the issue is that sometimes we go overboard in identifying the risk [when] it doesn't matter what group you're in [because] you have the same risk... (FG #3)

> [T]he bottom line is protecting the participant from the research-related risk, and if we put so much stuff in the consent form that they can't tell what the research-related risk really is, then we are not doing them any service by putting all that detail there. (FG #3)

Many IRB members were also concerned that the practical challenges of administering lengthy consent processes would negatively impact the ability to conduct research.

Alternatives to Consent—Focus group participants identified tensions between regulatory requirements and perceived patient needs and preferences. Some suggested that broad notification about ROMP would be preferable to requiring individual consent because the information would be more meaningful and easier to access.

> I think there are lots of times where an informational sheet is what you need to have and that's better than a legalistic consent. Again, this is a dichotomy between the regulations and what I think is best, but I think often an informational sheet that allows you to go to a website or something has more information or something would be much more informative for a family. (FG #3)

Others suggested that general patient education on ROMP and the learning health system should accompany a more streamlined consent process.

> I think families, patients, parents would be much happier with kind of the thinned-out model, which is a page or two of saying here's what we're proposing to do, here's what it means if you're in or you're out, and you don't have to be in if you don't want to... So I don't think we're facing a big issue. I think if we explain this comparative or learning healthcare system or comparative research, people will accept it. (FG #3)

Some IRB members noted the benefits of flexible conversations with patients.

> I think it's an interesting tension for me because I think I was really trained that there are actually risks of being too specific in things like side effects risks and benefits. So, for example, if you're going to do a surgery and you write down all the possible complications, that you're sort of implying that whatever is not written

> down is not going to happen to you. So if you forget at that time to write down for the patient that this might happen, as opposed to having a discussion that ideally is more of a conversation about risk and benefits, and maybe that's tailored to that patient. (FG #2)

Others, though they tended to agree with a less stringent approach to engaging patients, were concerned about the institutional implications of failing to meet regulatory requirements.

> I think that's a great idea but that's also when you get slapped down again by OHRP, or someone has their toenails fall out and they come back and say "but you didn't put it in the form," so we've got to change the regulatory approach to go "yeah, we didn't put it in there and we're not going to put it in there; it's not common enough." (FG #3)

Discussion

The growing expectation that healthcare systems will improve care not merely by adopting evidence-based clinical practices but also by using clinical care as an opportunity to increase knowledge makes it increasingly difficult to disentangle ethical obligations and oversight of research from those of clinical activities. Substantive ethical and policy questions are at stake. Among these, will the existing institutions for ethical research (and the rules they employ) be sufficient for ROMP or are new means of oversight needed? Our study suggests that IRBs are not prepared to take on this responsibility without substantial guidance on the key issues at stake in the ethics of ROMP—how to assess and evaluate incremental risk beyond the risks of usual care, and which approaches to consent and engagement are needed in light of those risks.

Taking Blurred Lines Seriously

Since our study reveals that IRB members see no clear distinction between clinical research and medical practice improvement, institutions planning to engage in ROMP face several significant challenges when it comes to interpreting regulatory oversight for research. On even our simplest question, whether ROMP should be reviewed by IRBs, no obvious consensus could be reached. Variation in practice and disagreements about key concepts such as "quality improvement" and "standard of care" make it difficult to know when activities constitute research and warrant IRB review. IRB members did identify some features of ROMP that might make such activities more characteristic of clinical research, such as intent to publish generalizable findings, the identification of clinical endpoints, and disseminating results to inform changes in wider clinical practice. Although consensus was not reached, these identified features are consistent with the definition of research outlined by the Common Rule as a systematic investigation designed to develop or contribute to generalizable knowledge (45 CFR §46.102). IRB members thought the harder questions in assessing risk and consent requirements surround randomization and, particularly, cluster randomization.

Guidance on research ethics in learning health systems will need to more explicitly acknowledge and address the erosion of the research-clinical practice boundary. Although some collapse in the distinction between research and clinical care may be unavoidable in

practice, a more interesting question is whether maintaining the distinction in principle is important. The ethical spirit of human subjects protection is to mitigate potential conflicts of interest between the aims of research and the obligations of clinicians to put care for patients first (Brody and Miller 2013). However, if as some have argued, we ought to use the best tools available to improve patient care—including classic research methods like randomization—it may be that we have a collective responsibility to participate in clinical activities that aim to improve health care (Faden et al. 2013; Lynn et al. 2007). The deeper issue is whether our ethical principles of responsible research and those of responsible patient care can somehow be brought together in this more overtly blended domain of research within usual medical care.

One specific way in which the blurred research-care distinction raised ethical concerns for IRB members echoed a dominant theme from our separate study of patients' attitudes, namely, that incorporating research into usual care might undermine the physician-patient relationship (Cho et al. 2015; Kelley et al. 2015). If the ethics of clinical care makes that relationship and its obligations central, and the ethics of research deliberately encourages some distance between the researcher and participant to avoid conflicts of interest, how should the IRB serve as an intermediary between these two very different ethical positions on the physician-relationships in the gray zone (Largent et al. 2011)? Similarly, if voluntariness in research serves as a protective cornerstone for participants, how are we to think of the more collective sense of responsibility to participate in quality improvement or comparative effectiveness research? Will designs promising patients the ability to "opt out" have any meaning in a context where their physician and the health institution see participation as an inherent component of the care they provide? People developing improved IRB guidance will need to give careful consideration to these and other substantive ethical issues, aided by further studies of stakeholders' views about research on medical practice. At the very least, our data suggest a very real barrier to maintaining clearly distinct domains between research and practice, and at times, deep confusion among IRB members over how to assess risk and consent in this context.

The Observer Effect: Does ROMP Introduce Additional Risks?

IRBs are expected to focus their review on the risks foreseeably created by research, which presupposes that such risks can be distinguished from those of usual care. However, our study reveals a substantial lack of consensus about what constitutes added risk, particularly when patients are randomized to different treatments identified within usual care. This suggests that if IRBs are expected to review activities associated with ROMP, analysts—and OHRP guidance—will need to address deep uncertainty about when and how the incremental risk of studying clinical care qualifies as a "foreseeable risk of harm" under the regulations. Our study suggests that IRB members are not at all clear how randomization of patients to approved clinical therapies in the context of ROMP differs from the distribution of these patients to the same therapies based on the variation in recommendations made by their physicians.

While variation and uncertainty in standard practices may justify the need for comparative effectiveness research, these types of studies pose a challenge for how to characterize the

risks of the proposed research vis-à-vis the baseline of varied "standard" practice (Magnus and Wilfond 2015). Importantly, there is substantial disagreement about how to distinguish the risk of ROMP from clinical care, even in straightforward cases when it is reasonable to assume patients would receive similar if not identical treatments. Much harder to evaluate are cases where patients are offered very different types of clinically warranted interventions (i.e., surgical vs. medical regimens). There is a kind of observer effect in ROMP: The real world of clinical medicine is varied, messy and full of uncertainty and risk. When we stop to carefully observe and compare those practices with an eye to improvement, do we alter the level of risk by virtue of observing it? The rise of learning health systems is likely to increase the quality of information available and thereby raise awareness about the day-to-day risks of clinical medicine. One of the more challenging tasks for IRB or other oversight bodies will be to carefully discern the added risks of research over and above the risks of clinical care.

Requirements of Consent: A Difficult Balancing Act

IRB members characterized the central challenge of ROMP review as balancing the need for full transparency of information for patients and protection of the physician-patient relationship, while avoiding a chilling effect on research that may result in important clinical benefits. Maintaining a distinction between research and practice remains important in the interpretation and implementation of human subjects regulations. Doing so recognizes that the relationships between patients and physicians and those between study participants and researchers differ not just descriptively but also morally. However, in learning health systems, the roles of physicians and researchers often overlap, which creates potentially divided commitments. This is a familiar tension in clinical research where physicians wear both clinician and researcher hats (Joffe and Miller 2008; Morin et al. 2002). Transparency is seen as essential to mitigating such conflicts and to preserving trust in physicians and hospitals. IRB members in our study voiced this sentiment. So the question was not *whether* to disclose but *how and what* to disclose. As long as there is disagreement about how to characterize the risks of ROMP, clarity will be lacking about what ought to be the content of consent or notification.

IRB members emphasized the need for balance. They expressed significant concern that including all the potential risks of research and usual care in extensive consent forms might overwhelm and confuse patients. While they stressed the importance of clarifying the risks of ROMP that IRBs and patients would need to consider, they emphasized the need for alternative approaches to traditional written consent for conveying information to patients. Indeed, patients might be open to alternatives. Our survey of the US general population suggested that many would be willing to forgo written consent if requiring it would make ROMP difficult to conduct (Cho et al. 2015). Similarly, a substantial minority recommended an alternative to written consent for participation in pragmatic randomized trials (Nayak et al. 2015). Our study reveals that effective approaches to consent must attend to the values of trust and transparency by balancing the need to provide sufficient, comprehensible information to patients with the goals of allowing ROMP to occur and of protecting the clinical relationship. One of the interesting and difficult questions for ROMP is whether having research activities so deeply integrated within day-to-day care alters our ability to go

beyond transparency of information and offer meaningful ways of opting out of such practices when they occur within the intimate folds of clinical care. Our participants said little about the issue of voluntariness in ROMP.

Implications for Future Research

As many in our study noted, the move toward learning health systems is already well underway. IRB members are being asked to deliberate in this confusing gray zone without much guidance. We can learn something important from these early attempts to evaluate ROMP. The lack of consensus expressed by IRB members indicates that varied decisions are being made about when and how to apply human subjects regulations to activities associated with ROMP. Achieving better and more consistent decisions will require clearer guidance about what to do about research in this new context. Research on IRB review practices across a spectrum of institutional settings is needed to identify how specific clinical contexts impact regulatory requirements for full disclosure of risks of research and related treatments. In particular, we need further research to determine how IRB members weigh the preferences of patients for consent and notification strategies in decisions to participate in ROMP. To address this gap, we developed an instrument aimed at probing our findings of uncertainty and lack of consensus in a national study of attitudes of IRB members towards ROMP. Other data suggest that many patients would find general notification acceptable if research could not otherwise be done (Cho et al. 2015). If patient preferences are more liberal than IRBs expect, it remains unclear to what degree IRBs would be willing to defer to patient preference and whether they could defer within current regulatory requirements (Cho et al. 2015).

Study Limitations and Conclusion

The primary goal of our qualitative data collection was to inform the design of a national public survey (Cho et al. 2015). As such, this study was not designed to achieve saturation on all issues, but rather to identify issues for survey development. Recruitment of study participants was limited to three academic research centers and did not draw from a national sample of IRB members. Our sample size is relatively small and as it is a convenience sample, we had limited control over racial and ethnic diversity or the breadth of research and clinical expertise among our research participants. While this was an exploratory qualitative study, participants offered a number of valuable insights to show the way forward. Even knowing where there is residual disagreement or lack of clarity is helpful in thinking about the work that needs to be done. As participants in our study noted, these changes are already happening in our hospitals and research centers. IRB members are being asked to deliberate in this confusing gray zone. Evidence-based guidance that supports IRB members engaged in the balancing act of providing adequate and effective oversight without impeding the research process or harming the physician-patient relationship is necessary to realize the full benefits of the learning health system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of Focus Group Participants (n=22)

Gender	
Female	15 (68.2%)
Male	7 (31.8%)
Age (years)	
Mean	59.5
Range	30–78
25th–75th percentile	54–69.5
Race	
American Indian or Alaska Native	0 (0%)
Asian	1 (4.5%)
Black or African-American	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)
White	20 (90.9%)
More than one race	0 (0%)
Prefer not to disclose	1 (4.5%)
Ethnicity	
Hispanic or Latino	1 (4.5%)
Not Hispanic or Latino	19 (86.4%)
Prefer not to disclose/no response	2 (9.1%)
Years on Current IRB	
Mean	7.09
Range	1–30
25th–75th percentile	3.25–9.5
Prior IRB Service	
Yes	6 (27.3%)
No	16 (72.7%)
Total Years on IRBs*	
Mean	8.3
Range	1–30+
25th–75th percentile	4–9.5
IRB Role**	
Chair	3 (13.4%)
Community Member	5 (22.7%)
Scientist	14 (63.6%)
Non-scientist	4 (18.2%)
Prisoner Advocate	0 (0%)

Other	1 (4.5%)
Occupation **	
Clinician, Adult	7 (31.8%)
Clincian, Pediatric	4 (18.2%)
Scientist	7 (31.8%)
Other	13 (59.1%)

* One participant listed service on current IRB as 30 years and total service as ">30 years," so the statistics for total years may be an underestimate.

** Participants were instructed to check all that apply, so percentages may sum to greater than 100%.

Table 2

	Major Themes and Subthemes	Representative Quote
1	**At the Heart of the Gray Zone: Is ROMP research and what makes it so?**	*The comparative effectiveness research trend sort of leaks into this quality improvement. What used to be just the quality improvement kind of scenario. [I]t's not very clearly defined differences anymore. (FG #1)*
2	**Uncertainty and Disagreement about IRBs' Obligation to Review ROMP**	*That would be my question, too- who gets to make the decision on when an information sheet goes out, and who makes the decision when it has to go back to the standard ethical review? Who makes the determination? It's just like with research in general, it just depends on every single study which is why we're burdened as much as we are. The regs are not ethics. (FG #3)* *Standard of care research probably should be reviewed but who and where? Is it IRB-based? Is it under the constraint of federal bureaucracy or is it just something you go to an ethicist and say hey, this is what we're going to do, is that cool? (FG #3)*
3	**Possible Risk of Receiving a Less Effective treatment**	*It elevates the paperwork, but if by some chance you're randomized to an arm that doesn't work for you or isn't the best for you, there's no way to know that in advance but that could happen. (FG #1)*
4	**Randomization Might Harm the Physician-Patient Relationship**	*Well, I just can't help but to bring it back to my husband, and he was given a choice by his physician, "Do you want A, B or C?" And he said, "Well I don't know...what do you think?" He says "well I'd probably choose this"...So it was all back to: he trusts me, he trusts the surgeon, and so patients do, and I've seen it watching him, really rely a lot on their surgeon, their doctor, their oncologist, whatever. (FG #3)*
5	**Lack of Consensus on Consent**	*I think it's important also that people don't feel like they're locked into whatever because they're in a study and it's studying the standard of care. That just because they got assigned drug A and all of a sudden they have really bad side effects that they have to take drug A for the rest of their life. The same thing that we have in all the consent forms—that you can withdraw from the study even it's a study of medical practice as opposed to other types of experimental studies. (FG #1)* *[regarding disclosure of randomization] Oh, I'm not sure if you're really required to tell a patient that that's what you're doing. (FG #2)*
6	**Agreement on Transparency**	*As I define ethics, one component of it is surprise. Don't surprise me. If we talked and it might happen, okay, I went into it. But, if you say nothing and it happens, we've got a problem when you could have told me. (FG #1)*
7	**Disagreement about which risks should be disclosed**	*I would think you still have to talk about the risk of standard practice because for the person who is deciding whether or not he or she is going to participate, they kind of need to see that. (FG #3)* *Disclosing all of the potential risks of the standard of care procedures would be more confusing than helpful, because that's going to happen to them whether they're in the trial or no. [W]hat you really should focus on is why we're doing the study; 'these are the things that we're thinking about that might be better or worse about these two treatments that we're comparing'. (FG #3)*
8	**Tradeoff between Transparency and Too Much Information**	*I think it would be a disaster... I think it would just bog it down; it would stop it. You'd have so much information that you wouldn't know what to do with it and how to cut it. And I'm a proponent of informing a patient, and I say don't do it. (FG #1)* *Some of the QI work, if you require a very formal process of consent, it's not gonna be done. For one thing, who's gonna do it? Who's gonna pay for it? It's just not gonna happen. So then you're just defeating the research.... I think if it really significantly impairs the ability of the research to go on, then you have to relax what you're gonna require because there is benefit to QI research, and we can't just be stonewalled in everything and never make any progress. (FG #2)*