Stakeholder perspectives regarding alternate approaches to informed consent for comparative effectiveness research

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Abstract
Introduction: Traditional informed consent approaches, involving separate discussions and lengthy consent forms, may be an imperfect fit for comparative effectiveness research (CER) that is integrated into usual care and compares non-investigational treatments. However, systematic efforts to collect broad stakeholder perspectives about alternative streamlined approaches to disclosure and consent in this context have been limited.

Methods: We used a deliberative engagement method to solicit the views of a multi-stakeholder group regarding 3 alternative models of disclosure, consent, and authorization in CER studies: Opt-In, Opt-Out, and “General Approval”. Participants considered the acceptability of these 3 models for observational and randomized CER studies of hypertension medications and for alternative treatments for spinal stenosis, all conducted in the context of a learning health care system.

Results: Fifty-eight stakeholders participated in the all-day deliberative engagement session. Following deliberation, a majority of stakeholders (67%) liked the General Approval model for the observational hypertension study, more than the number who reported liking Opt-Out or Opt-In (45% and 36%, respectively). Support was lower for General Approval model in the context of a randomized hypertension study, with 80% liking a traditional Opt-In approach, compared with 54% liking Opt-Out, and 11% liking General Approval. Similarly, for the spinal stenosis CER studies, while most stakeholders preferred a streamlined Opt-Out approach for the observational design, most preferred a traditional Opt-In approach for the randomized version.

Conclusions: This multi-stakeholder group was more favorable towards streamlined models for disclosure and authorization for observational CER than randomized designs. These findings are consistent with arguments that informed consent requirements should be tailored to the context of the research design, rather than a standard “one size fits all” approach.

KEYWORDS
informed consent, comparative effectiveness research, learning health system

INTRODUCTION

Comparative effectiveness research (CER) and patient-centered outcomes research (PCOR) studies are increasingly being conducted to better understand existing therapies, many of which have been used in routine clinical practice for decades. CER/PCOR studies are often embedded in usual care settings, designed both to produce results that reflect real-world care environments, and to facilitate recruitment of the larger cohorts needed for comparing non-investigational treatments. This research is consistent with a broader interest in moving
towards a learning health system (LHS), involving a bidirectional feedback loop whereby data collection is embedded into care delivery processes, and this evidence is used to improve care.5

These features of CER/PCOR studies have prompted questions regarding the appropriateness of traditional informed consent mechanisms. Requirements for informed consent for research in the United States have a deep and important history, with regulations requiring consent for most studies having been promulgated after a series of unconscionable examples of research conducted without consent were brought to the attention of the American public.3 However, some scholars have suggested that traditional consent procedures may not be ethically required in certain CER/PCOR contexts, such as when the treatments being compared are non-investigational and low risk, and differ from one another in ways that are not generally relevant to patients.4,5 Others have noted that traditional consent procedures are both complex and time-consuming, and may unnecessarily hinder research, thereby compromising the generation of important new knowledge, especially as CER moves from conventional research contexts to busy clinical practices.6 Such critiques have led to various proposals for streamlined options for disclosure to patients and authorization.3,7-9 However, little consensus yet exists regarding the conditions under which such alternatives would be ethically permissible.10-12

Recent empirical studies suggest patients may be open to alternate approaches to disclosure and consent in some CER/PCOR contexts.13-17 A more limited number of studies have explored the views of Institutional Review Board (IRB) professionals16,18 and physicians19 regarding informed consent for CER/PCOR; however, the perspective of the broader range of stakeholders involved in CER/PCOR remains underexplored.

Building on earlier work,12,17 we sought the views of a multi-stakeholder group on alternate approaches to disclosure and consent for 2 different types of CER/PCOR studies. We convened a deliberative engagement session (DES) to examine diverse stakeholders’ perspectives about the acceptability and potential challenges associated with alternate models of informed consent, disclosure, and authorization for CER/PCOR studies, and whether those perspectives changed in the context of a LHS.

2 | METHODS

The Center for Medical Technology Policy and the Johns Hopkins Berman Institute of Bioethics hosted a full-day, in-person, DES12,20 in April 2014 in Baltimore, MD with a broad sample of health care stakeholders. This multi-stakeholder DES was part of a larger study that used the same methods to capture patients’ views on this topic.12,21

2.1 | Stakeholder identification and recruitment

The research team identified 7 broad stakeholder categories relevant to the question of informed consent for CER/PCOR: (1) Patients and Patient Advocates, (2) Clinicians (physicians and nurses), (3) Ethical and Regulatory Research Oversight (eg, Directors of Research Integrity and/or Bioethics Programs for major health care systems, IRB chairs, HIPAA attorneys), (4) CER/PCOR Researchers, (5) Health Care System Administrators, (6) Payers (clinical and administrative leadership from both public and private insurers), and (7) Research Funders (public and private). Relevant organizations and individuals were identified from Center for Medical Technology Policy’s professional contact database, other professional contacts, and the internet. Stakeholders were invited via email to participate in a full-day multi-stakeholder meeting. Patients and patient advocates were oversampled.

2.2 | Deliberative engagement session method

The DES followed the approach described by Kass et al.12 We held a 1-day, structured session in which short plenary presentations alternated with small group stakeholder discussions. Plenary presentations provided information on (1) CER, (2) the LHS (Exhibit 1), (3) 2 hypothetical observational and randomized CER studies, one comparing hypertensive medications and one treatments for spinal stenosis (Exhibit 2), and (4) 3 approaches to disclosure/consent for CER (Exhibit 3). The 2 CER studies were selected to assess whether stakeholders perceived a difference between a study (hypertensive medications) anticipated to have no or minor effects on patient interests such that patients would be unlikely to have a preference for 1 medication over another, and another (spinal stenosis) in which the 2 options have different implications for patients’ lives and thus about which patients

| EXHIBIT 1 Description of learning health care system (LHS) | EXHIBIT 2 Describe 2 CER studies and their comparative research importance | EXHIBIT 3 Display 3 ways to disclose/consent information |
might have preferences, even in the absence of evidence about which is more effective. After each plenary, stakeholders discussed the information at assigned, round tables of 6 to 8 diverse stakeholders, along with a facilitator and notetaker. Early discussions aimed to ensure that all stakeholders understood the key topics. Later sessions aimed to explore stakeholders’ views regarding which disclosure and consent models they found acceptable and which they preferred for observational and randomized study designs for each of the 2 studies presented.

2.3 Quantitative data collection and analysis

Upon arrival at the DES, participants completed a pre-test survey on an iPad. The survey collected demographic characteristics, professional characteristics (eg, stakeholder type), and attitudes towards the 3 disclosure/consent models as applied to 2 hypothetical CER hypertension studies (1 randomized, 1 observational). The 3 disclosure/consent models included (1) a “General Approval” approach where patients are informed that their health system routinely conducts certain types of low-risk CER, but patients are not notified regarding individual studies nor are they given an opportunity to opt out of participating, (2) an “Opt-Out” approach where clinicians provide a brief description of the study and patients are told they will be included unless they say they do not want to participate, and (3) a traditional informed consent or “Opt-In” approach where patients are given extensive oral and written information about the study and can only participate if they give their written permission. At the end of the day, participants completed a post-DES survey assessing attitudes towards the 3 models, using the same iPad to enable analysis of paired responses. Survey data were analyzed using SAS version 9.3 and STATA version 12. Attitudinal responses were collapsed into dichotomous categories: “liked” (“somewhat” or “very much” liked) and “didn’t like” (“neutral”, “somewhat disliked”, or “really disliked”). McNemar’s test was used to compare paired pre-DES and post-DES responses.

2.4 Qualitative data collection and analysis

Following presentations of the hypothetical observational and randomized studies, the small groups discussed: (1) which of the 3 disclosure/consent models they found acceptable, (2) which they preferred for each study design, and (3) whether their opinions would be different in the context of a LHS. In addition, small group breakout sessions discussed preferences among the disclosure/consent models for a study (not included in the quantitative survey) comparing minimally invasive surgery to epidural steroid injections for lower spinal stenosis.

All small group discussions were audio-recorded and transcribed. De-identified transcripts were checked for accuracy and uploaded to NVivo10. Transcripts were independently coded by 2 study team members following a codebook developed for a previous study and then reviewed by a third analyst to confirm and promote consistency of interpretation. Transcripts were coded for participants’ attitudes towards the disclosure/consent models (eg, positive, negative, ambivalent), for reasons supporting their attitudes, and for explanations for changes in opinions. Coded texts were categorized into overarching themes.
3 | RESULTS

3.1 | Study participants

Fifty-eight stakeholders, distributed among 8 small groups, participated in the DES. Among these, 28% identified their primary role as patients or patient advocates, and 21% as researchers. The remaining represented a mix of clinicians, health system administrators, research oversight experts, payers, and research funders (Exhibit 4). The group was evenly split between men and women, and the vast majority of participants (93%) were between the ages of 40 and 69.

3.2 | Quantitative results

Fifty-five of 58 participants completed both the pre-DES and post-DES surveys. For the observational hypertension study, 34% of respondents liked General Approval before deliberation, compared with 65% and 56% that liked Opt-Out and Opt-In, respectively (Exhibit 5). Following deliberation, 67% liked General Approval for this study design, 45% liked Opt-Out, and 36% liked Opt-In (P < .01 for all pre-post comparisons).

EXHIBIT 4 Stakeholder participant characteristics

| Stakeholder Type (Multiple Selections)* | n (%)
|----------------------------------------|------
| Patient, patient advocate, or consumer | 26 (45)
| Clinician (practicing physician or nurse) | 18 (31)
| Health system administrator | 9 (16)
| Research oversight expert | 12 (20)
| Payer | 7 (12)
| Researcher | 25 (43)
| Research funders | 9 (16)
| Other† | 6 (10)

*counts and percents will not add up to 58 (100%)
† “cancer survivor,” “compliance,” “bioethicist,” “consultant,” “institutional legal”

EXHIBIT 5 Pre-post responses to consent models (Like vs Neutral/Dislike)

| Observational Case Study | Like (Somewhat or Very Much) This Way | Neutral or Dislike (Somewhat or Very Much) This Way | P-Value
|--------------------------|-------------------------------------|-----------------------------------------------|-----
| General Approval | n (%) | n (%) | <0.001
| Pre | 19 (34.5) | 36 (65.5) |
| Post | 37 (67.3) | 18 (32.7) |
| Opt-Out | n (%) | n (%) | 0.005
| Pre | 36 (65.5) | 19 (34.5) |
| Post | 25 (45.5) | 30 (54.5) |
| Opt-In | n (%) | n (%) | 0.008
| Pre | 31 (56.4) | 24 (43.6) |
| Post | 20 (36.4) | 35 (63.6) |
| Randomized Case Study | n (%) | n (%) | 0.480
| General Approval | n (%) | n (%) | 0.808
| Pre | 8 (14.5) | 47 (85.5) |
| Post | 6 (10.9) | 49 (89.1) |
| Opt-Out | n (%) | n (%) | 0.655
| Pre | 29 (52.7) | 26 (47.3) |
| Post | 30 (54.5) | 25 (45.5) |
| Opt-In | n (%) | n (%) | 0.005
| Pre | 45 (81.8) | 10 (18.2) |
| Post | 44 (80.0) | 11 (20.0) |

For the randomized hypertension study, respondents’ views did not change significantly between the pre-DES and post-DES surveys. Both before and after deliberation, fewer than 15% liked General Approval, approximately half liked Opt-Out, and 80% liked Opt-In.

3.3 | Qualitative results

Discussions about the hypertension study differed somewhat from those about the spinal stenosis study. Each is described later.

3.3.1 | Case study 1: research to compare medications for hypertension

The majority of stakeholders preferred General Approval for the observational hypertension study. The most common explanation provided was that, assuming proper data security, this study involved no risk to patients. In explaining this choice, some noted that observational studies are regularly conducted without individual consent. An additional explanation put forward by several stakeholders was that General Approval would improve data quality, as it would include more patients than the other models. A few also suggested that there is a moral obligation to participate in this research. As stated by 1 participant: “I feel like it’s a moral obligation to make your data—the details of your health—available for research, because we need that to be able to succeed and to improve.”

A sizable minority favored Opt-Out for this observational study. These participants felt that individual patients should know about specific studies, even for purely observational research, to maintain transparency and respect autonomy. As described by 1 participant: “I would not find [General Approval] acceptable in an observational study just because I would want more transparency. There is a question out there and there are two different medications that could possibly help me...I
would like to know more information about that." A few participants noted that, even if most people would find General Approval acceptable, some individuals would be unhappy to learn that information about them was used without their permission. Participants favoring Opt-Out also raised concerns about the quality and accessibility of information provided via General Approval. A few described General Approval as "meaningless" as there is no way to ensure that patients access or understand the information provided. These participants also raised equity concerns, as some patient subpopulations may be more likely to access and understand the information than others.

Five participants stated that Opt-In should be required for the observational study, but provided different explanations. Three favored Opt-In as a means to ensure information was delivered appropriately and to foster transparency and trust. One emphasized the value of shared decision-making in all interactions. Another argued that it is an "ethical violation" to disclose patient information (even if de-identified) without express, written consent.

In considering the appropriate model for the randomized hypertension study, there was little support for General Approval. Participants were split fairly evenly between those who preferred Opt-Out versus preferring Opt-In.

Participants who favored Opt-Out justified this streamlined option because of the risk equivalence of the 2 medications, and physician equipoise regarding effectiveness. They felt that randomization required some form of individual disclosure, but thought a brief process with opportunity to refuse would suffice. As one described: "For the randomized trial in this case, if these treatments are truly felt to be—we have no idea which one is better—I’d be comfortable with [Opt-Out] just because the randomization process, I don't think, poses any other risk than the patients have going to a physician and being subject to their idiosyncratic decision making.”

Another participant suggested that Opt-Out is a more honest approach, because, as she described, "...I do not think that physicians are very good at always describing their uncertainty to patients. I think that introducing these types of trials as an opt-out design really makes it clear for the patients that the provider thinks [they are] appropriate for this trial..."

A few participants who favored Opt-Out in this scenario referenced potential benefits for recruitment and implications for data quality. As one explained: "I would still come down [for Opt-Out] because I think, again, this issue of opting in is a challenge in terms of getting sufficient sample size."

Nearly all participants favoring Opt-In for the randomized study characterized randomization as interfering with physician-patient decision-making. As one described: "...even if it’s the same decision the clinician would have made, and they truly are equal...if there’s somebody other than the clinician that I went to and hired and trust making that decision, then I think that kicks it up a level, even if the outcome is no different."

At one table, participants favoring Opt-In discussed the distinction between arbitrary and random in explaining their decisions. They acknowledged that clinical decisions often have a degree of arbitrariness, but suggested that decisions nevertheless reflect professional experience. A few people also noted that physicians are likely to suggest the treatment they have the most experience with, and that there may be some level of increased risk associated with lack of experience administering a particular treatment.

Furthermore, despite acknowledging the value of CER and lack of knowledge regarding which medication is best for which patients, there were stakeholders at every table who sought to identify other ways besides efficacy or safety, such as cost, quality of life, or patient-reported outcomes, that the medications might differ, and which would be important to patients.

A number of participants favoring the Opt-In model questioned the validity of the Opt-Out approach, in that there would be no way to know what was communicated to the patient. They felt that Opt-Out represented an ethical compromise motivated by researchers' desire to increase enrollment. According to one: "So most opt-outs I think are a little underhanded... if you’re truly actively opting-out that's one thing, but I don't think in most cases that’s what happens. In general what I'm really concerned about is how the hell am I supposed to know... that my doctor is delivering it the right way?" Others suggested that Opt-Out is unduly coercive because patients may find it difficult to say no to their physicians, fearing that doing so would negatively impact their care.

A common theme in several group discussions was that the question of whether someone has to opt-in or opt-out for a particular study is less important than the opportunity to make a decision. As stated by 1 participant: "...and I think the opt-in and opt-out is a distraction...The issue is informed consent is needed. Whether you opt-in or out is irrelevant."

Several people suggested that there should be no difference in the amount of information provided for Opt-Out versus Opt-In, and that patients should always have sufficient information about the risks and benefits, and adequate time to make a reasoned decision about participation. In addition, many participants expressed displeasure with the current approach to informed consent and supported more patient-centered approaches that value understanding over legal protection.

For the hypertension studies, participants were asked to reflect on whether the context of a LHS changed their views about disclosure and consent. The largest change was that half of participants who initially favored Opt-Out for the observational study indicated that they would find General Approval acceptable in the LHS context. One participant who changed her opinion described it this way: "...[my view] has changed because I’m assuming an educated patient population and a living institutional or clinical environment for sharing and I think that General Consent would be acceptable for the observational study." Another participant compared the LHS to a teaching hospital: "...my care might be by a student and there's going to be a physician back there but the students are going to work on me today, and that's just your understanding when you go there. So my understanding when I go to a learning health system is I'm part of research now."

The shift to viewing General Approval as acceptable was contingent on a LHS that clearly meets the description provided with regard to engagement, transparency, and accountability (Exhibit 3). Several participants indicated that they would be more comfortable with General Approval if patients were given an opportunity to opt-out of all research when they enter the system. Some feared that, without this option, patients who were unable to choose a different
health system due to financial or other reasons would be forced to participate in research.

There were minimal changes in opinion with regard to the randomized study, although a few participants did indicate that they would find General Approval acceptable in the context of a LHS. Many participants indicated that, although their preferred model would not change, they would feel much more comfortable with Opt-Out in a true LHS environment.

Regardless of opinions towards the models, the group as a whole responded very favorably to the concept of a LHS. They saw great value from ongoing patient engagement in the research process to improve study design and communication surrounding research. This favorability did not necessarily translate into support for the concept of an "ethics board." There was confusion regarding how such a group would be differentiated from the IRB, and some emphasized that it is more important to change the culture of the health system as a whole rather than to add a new component to the infrastructure.

3.3.2 Case study 2: research to compare alternative treatments for spinal stenosis

Opinions about the best model for the observational spinal stenosis study were similar to those expressed for the hypertension study, with most preferring General Approval. Several stakeholders noted, however, the likelihood of needing more, and possibly more sensitive, information from patients to adequately address this research question. These stakeholders suggested that even the observational design would therefore require patient contact and, consequently, some kind of individual disclosure/consent.

The vast majority favored Opt-In for the randomized spinal stenosis study, including most who had favored Opt-Out for the randomized hypertension study. In explaining the difference, participants pointed to the higher level of risk associated with this study, the difference in level and type of risk between the 2 study arms, and the risk that patients would be randomized to a study arm that is inconsistent with their personal preferences. As described by 1 participant: "Even if the treatments... are equivalent, you’re in a space where there’s— it’s a high risk space. Either way you go, it’s a high-risk space you’re in. And people value things differently in high-risk spaces."

Participants in 1 group also discussed the distinction between consent to randomization and consent to treatment. They suggested that the consent to treatment would be required for both treatment options, and that this would provide an additional layer of patient protection and respect for autonomy. In other words, patients would have a second opportunity to decide about how their treatment would proceed, as they would be asked for their consent to be randomized and for their consent to the particular treatment to which they would be assigned.

4 DISCUSSION

The primary aim of this study was to provide empirical information from a multi-stakeholder group regarding the perceived acceptability of 3 models of consent and disclosure for CER/PCOR studies. We sought to explore multi-stakeholder views for observational and randomized CER designs, within the context of a more straightforward (hypertension) and a more complicated (spinal stenosis) CER topic, and for CER conducted in the context of a learning health care system with commitments to engagement, transparency, and accountability.

In considering appropriate models of disclosure/consent for prospective observational CER for hypertensives, nearly 70% of stakeholders liked General Approval following deliberation. In this model, research studies would be described on websites and in patient newsletters, but study information would not be actively provided to individual patients and there would be no opportunity to opt out. Support was nearly twice as high for General Approval for an observational CER study for hypertensives after deliberation as it was before, suggesting the DES method may have influenced multi-stakeholder attitudes toward streamlined consent approaches for CER. Notably, the majority of stakeholders also preferred General Approval for observational research for spinal stenosis.

In justifying their preference for General Approval, participants described both the minimal risk to the patient, and the benefit of more robust research findings. Several also described the observational study design as essentially mimicking current policy regarding record review research, already allowable without either disclosure or consent.

Our study found stronger support for General Approval in prospective observational studies than did prior surveys with patients or the general public. For example, while over two-thirds of this multi-stakeholder group supported General Approval for an observational hypertension study following deliberation, only half of participants in an earlier patient-only DES did so. One possible explanation for this difference is that stakeholders may be more aware than patients or the general public of the goals and importance of CER and how different consent approaches may affect the pace, cost, or quality of CER. There is some support for this interpretation in an earlier survey by Cho et al in which increased patient understanding of a possible consent/evidence tradeoff resulted in more support for a general disclosure model. Additional support is offered in qualitative work by Kraybill et al in which patients with serious health conditions seemed to be more open to streamlined approaches than the general public. It is possible that seriously ill patients are like other health care stakeholders in placing more weight on advancing research than other values, such as privacy.

The stronger support for General Approval in this study may also reflect a greater awareness of existing norms governing research among this multi-stakeholder group as compared with members of the general public, particularly norms allowing medical record research to frequently proceed without any patient notification. Although some participants in the multi-stakeholder DES brought a patient perspective, they were often experienced patient advocates with potentially greater knowledge about the health care system and existing regulations; their advocacy background also may have meant they brought stronger commitments to advancing research than patients in general. These findings underscore the importance of educating patients and other stakeholders on the motivations for conducting research within the context of care delivery and the relevant tradeoffs associated with different consent approaches, including the implications of different consent approaches for the generation of evidence to improve care delivery.
Our stakeholders were less supportive of streamlined approaches for randomized designs. By contrast, our earlier DES study of disclosure/consent preferences among patients found no difference in support for streamlined approaches for randomized studies as compared with observational designs.\textsuperscript{12} These findings are consistent with those of Kraft et al, who found that, while patients generally had similar consent preferences for both observational and randomized studies, IRB professionals distinguished between different study designs when expressing preferences regarding approaches for disclosure/consent.\textsuperscript{16} One explanation for this difference, suggested by prior qualitative work, is that IRB professionals may view observational research as less risky than randomized trials.\textsuperscript{24} Qualitative comments from our participants support this hypothesis. Our qualitative data also suggest greater sophistication concerning research methodologies among diverse stakeholders than among patients or the general public, as well as potentially greater appreciation of other ways that randomization affects decisions about the course of treatment and patient values—distinctions which may have influenced their preferences regarding disclosure/consent approaches. For example, our stakeholders were able to identify other possible differences, such as differences in cost, that may influence patients' preferences for 1 treatment over another. They also noted that Opt-In is particularly important when treatment options involved are different in kind or degree of risk or other characteristics that may be important to an individual patient or clinician.

In contrast to earlier studies in this area, we explicitly grounded our discussion of disclosure/consent models within the context of a LHS. Notably, the LHS context did not substantially affect our participants' attitudes towards disclosure/consent models for randomized CER studies. Nevertheless, some participants indicated that the parameters outlined by the hypothetical LHS might make them more comfortable with a streamlined approach to disclosure/consent for observational studies. To the extent that the LHS delivers on the promise of greater engagement, transparency, and accountability, stakeholders may be more open to alternative and streamlined approaches to disclosure/consent and also possibly research oversight.

Our findings provide insights into how diverse stakeholders think about disclosure and consent for CER, including the features of research that are important to them. However, they should be interpreted in light of several limitations. First, these results are based on a single multi-stakeholder DES; we do not know whether similar findings would be replicated with different or larger stakeholders groups. Second, this study design did not allow us to detect differences in opinion by stakeholder subgroup nor, in most cases, to know the stakeholder identity of a participant quoted on a small group transcript. Third, racial and ethnic minorities were underrepresented among stakeholders attending the DES. While the research team sought to recruit a diverse group of individual stakeholders, our efforts were limited by our networks of existing contacts, and the degree of flexibility of stakeholders' work schedules to attend a full-day meeting in Baltimore. Consequently, some viewpoints may have been overlooked. Finally, we situated our discussion in the context of a hypothetical LHS. While this context may be instructive for health care systems looking to improve research and care integration, some stakeholders had difficulty envisioning health care settings beyond the current US health care and research paradigm.

5 | CONCLUSION

As more research is embedded into busy clinical care settings, discussions about what type of disclosure and consent is appropriate become increasingly salient. Our study suggests that stakeholders involved in and affected by CER may be open to streamlined approaches to disclosure in some contexts. In considering streamlined approaches, stakeholders familiar with CER weigh a range of considerations, including whether study design increases risk or otherwise affects patient care, as well as the potential impact on research efficiency and resulting data quality.

Our results lend support for arguments that informed consent for research is not a "one size fits all" process, but instead should be tailored to context.\textsuperscript{11} Moving forward, additional empirical work can help clarify the relevant tradeoffs, and identify when and in what circumstances stakeholders are willing to accept streamlined approaches in order to support other values, such as increasing generalizable knowledge and advancing research to improve health.

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