Author's response to reviews

Title: Quality Improvement, Quality Improvement Research, Ethical Oversight and Learning Health Care Systems

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QUALITY IMPROVEMENT, QUALITY IMPROVEMENT RESEARCH,
ETHICAL OVERSIGHT AND
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ABSTRACT

**Background:** Institutional review boards (IRBs) distinguish health care quality improvement (QI) and health care quality improvement research (QIR) based primarily on the rigor of the methods used and the purported generalizability of the knowledge gained. Neither of these criteria holds up upon scrutiny. Rather, this apparently false dichotomy may foster under-protection of participants in QI projects and over-protection of participants within QIR.

**Discussion:** Minimal risk projects should entail minimal oversight including waivers for informed consent for both QI and QIR projects. Minimizing the burdens of conducting QIR, while ensuring minimal safeguards for QI projects, is needed to restore this imbalance in oversight. Potentially, such ethical oversight could be provided by the integration of Institutional Review Boards and Clinical Ethical Committees, using a more integrated and streamlined approach such as a two-step process involving a screening review, followed by a review by committee trained in QIR. Standards for such ethical review and training in these standards, coupled with rapid review cycles, could facilitate an appropriate level of oversight within the context of creating and sustaining learning health care systems.

**Summary:** We argue that QI and QIR are not reliably distinguishable. We advocate for approaches that improve protections for QI participants while minimizing over protection for participants in QIR through reasonable ethical oversight that aligns risk to participants in both QI and QIR with the needs of a learning health care system.

**Keywords:** Ethics, Research  Research Subjects  Ethics, Committees Research  Health Services Research Quality Improvement  Ethics Clinical Learning Health Care System
BACKGROUND

In a provocative pair of articles, Kass et al and Faden et al argue that the research-treatment distinction is no longer tenable, and propose new ethical principles for guiding both research and treatment in the context of a learning health care system.\textsuperscript{1,2} Their proposed principles regard the failure to use information gathered from the point of care for research and learning as unethical. However, their papers leave open the question of how to begin such reform. Actionable next steps under current regulations are uncertain.

Our experience with many research and quality improvement research projects has prompted us to reflect on these complex issues and propose concrete next steps that might be adopted under the current ethical regulations for research. We focus on the interface between quality improvement research (QIR) and quality improvement (QI). We argue that QIR and QI are indistinguishable; that they are sufficiently distinct from other types of clinical research that they warrant their own distinct processes and committees for ethical oversight and that the level of oversight should balance risk to participants with an ethical imperative to improve care.

DISCUSSION

Existing guidelines distinguish QI and Research

The United States Department of Health and Human Services (DHHS) regulates biomedical and behavioral research ethics in the United States under the Common Rule. It has remained largely unchanged since 1991 and reform appears stalled.\textsuperscript{3} Both the Common Rule and World Health Organization (WHO) guidelines attempt to distinguish QI and research.\textsuperscript{4} This is understandable based on concerns that placing QI under The Common Rule could hinder processes designed to improve patient care and ultimately reduce patient risk.\textsuperscript{5}

QI And QIR Are Not Reliably Distinguishable

The Common Rule, WHO guidelines, and consensus statements have sought to distinguish research and QI based on the rigor of methods (internal validity) and generalizability (external validity) of the findings.\textsuperscript{4,6} On close inspection, these criteria alone do not hold up.

Rigor of methods
Traditional research methods, and the methodological rigor they represent, enhance the internal validity of the findings whether considered research or not. That is, they improve confidence that the findings are valid for the population(s) under scrutiny. However, high internal validity is not unique to research including quality improvement research (QIR). Rather, use of rigorous methods is based on two often competing goals. The first goal is minimizing type I error (essentially a false positive finding or inferring an effect exists when none actually exists) as well as type II (a false negative finding or inferring no effect exists when one actually exists). The second goal is feasibility of the methods. Feasibility issues include technical, methodological (e.g. types of design) operational (e.g. effects on workflow), costs, and acceptability to patients, providers, administrators, and communities. A desire to reduce invalid inference, whether type I or II errors, apply to both QI and QIR. For example, a large, national health plan conducting QI might have a strong desire to minimize type I error through use of highly rigorous methods including randomization, while also minimizing type II error, through sufficiently large sample sizes, before rolling it out to all plan members. As with QIR, QI must balance strong methods against feasibility. The competing goals of getting the correct answer with practical constraints alone do not clearly distinguish QI and QIR.

The risks associated with invalid findings, whether QI or QIR, have important ethical implications. Both entail costs and potential burden to participants, and the possibility of risks to future patients. Use of less rigorous study designs, i.e. those associated with a higher risk of confounding that may result in spurious findings and invalid inferences, means that research and/or healthcare resources are potentially squandered and that participants are exposed to unnecessary risks and burdens (however minimal) with the possibility of little or no benefit, or even the possibility of harm, particularly where understudied subgroups experience paradoxical effects.

Generalizability of findings

The second major criterion, generalizability (external validity), is also problematic in distinguishing QI from QIR. First, QI and QIR (and other pragmatic research) often involve use of “real world” settings and participants. In contrast, traditional clinical research is often much less generalizable.\(^7\)\(^8\) A traditional randomized controlled trial with a long list of highly selective eligibility criteria may yield findings that are less generalizable than a QI intervention conducted with patients with fewer or no eligibility restrictions, particularly those that exclude patients with multiple comorbidity. Traditional randomized controlled trials are often intended to generate generalizable knowledge of a different sort, i.e. scientific principles, mechanisms, processes or theory. Nonetheless, in terms of extrapolation of findings regarding the intervention itself, these trials often have poor generalizability.\(^9\) In contrast, QIR trials often examine patient
populations similar to those used in QI projects. In both cases, the selection of
participants is based on the level of generalizability, i.e. to other patients in a system or
more broadly to similar participants.

The second challenge to generalizability as a distinguishing feature is that
generalizability represents a broad continuum without clear lines of demarcation. Most
QI findings are intended to generalize beyond the immediate participants and
healthcare delivery systems and practice settings. A large health plan or large hospital
system might conduct a quality improvement project within several geographic regions
with the hopes of generalizing the findings nationally. Depending on the context and
unique features of the organization, the findings may or may not be generalizable to
other plans and practice settings. Similarly, few QIR projects involve a sufficiently large
or diverse populations of patients, clinicians and practices to have ensured widespread
generalizability and replicability.

The generalizability conundrum is not remedied by resorting to the stated intent of the
project. Asking the project leaders whether they intend to generalize their findings (i.e.
knowledge gleaned) beyond the participants is misleading. QI projects invariably involve
some degree of generalizability, even if it is limited to the population served by the
institution that generates the findings from a sample of observed patients. This may
include extrapolation of findings to concurrent non-participating patients or to future
patients. In contrast to QI leaders, QIR leaders often overestimate the generalizability of
their findings and minimize threats to external validity.¹⁰ In addition, stated intent may be
distorted to reflect the desire of expediency based on avoiding IRB review or based on
journal requirements for IRB review. In sum, generalizability is a continuum without
clear cut-offs that reliably distinguish QI for QIR.

Other Criteria

Other proposed criteria for distinguishing QI from research similarly do not reliably
distinguish QI and QIR. Casarett et al suggest that a project should be deemed
research if a majority of patients involved are not expected to benefit.¹¹ These criteria
are more helpful in distinguishing QI from traditional clinical research than from QIR,
which potentially entails as much direct benefit to participating patients as QI projects.
Given the absence of standards for implementing QI, there is no a priori reason to
believe that expected benefit would be greater with QI than with QIR.

Whether a project imposes additional risks and burden to improve generalizability
represents a second criterion proposed by Casarett et al.¹¹ It too fails the test.
Pragmatic research including QIR, strives to avoid undue burden on participants.⁸ Other
proposed criteria, including as source of funding, plans for publication and
dissemination, and involvement of researchers in the project,¹² are arbitrary and not
Balancing competing ethical principles

If QI and QIR are not readily distinguishable, then what are the implications for ethical oversight? How should ethical oversight be balanced with the need to create continuous learning healthcare systems? When is informed consent by patients necessary and under what conditions is informed consent required from clinicians and other staff? With the increased attention to “pragmatic research” using electronic health records, under what conditions is a waiver of informed consent necessary and reasonable? In the remainder of this paper, we address these questions.

Risk to participants versus the imperative to improve care

The level of scrutiny should balance the risk participants with the need to expedite care improvement including an ethical imperative to learn quickly. This balancing of competing ethical principles should be the primary task rather than seeking to resolve an arbitrary distinction between QI and QIR. Currently, most large QI projects appear to undergo some level of review, particularly with regards to participant risk and confidentiality of data. However, the quality of this review may be variable and typically ill defined. Length of IRB reviews among the same QI and QIR projects vary widely. Standardization of oversight for QI and QIR is needed. This approach would help prevent future mishaps, e.g. suspensions national QIR projects.

Ethical review considerations

Unlike current QI reviews (which are often internal), ethical oversight reviews including those for QI should be independent and should reflect bioethical and methodological expertise, and perspectives from administrators, clinicians and patients. Ethical review should consider soundness of the methods, including whether the methods are sufficiently rigorous to meet the goals and scope of the project and minimize invalid inferences. An ethical review for QI and QIR would not preclude use of rapid cycle or Plan-Do-Study-Act (PDSA) approaches that are fundamental to learning healthcare systems, but would help to ensure appropriate use of resources, as well as protection of patient privacy and safety.
Ethical oversight can be provided using current institutional oversight committees with some modifications. It would mean creation of a separate committee to review QI/QIR projects. Provided that current ethical guidelines for research, e.g. “The Common Rule” are followed, and that reasonable criteria for minimal risk criteria are applied, QI and QIR could be reviewed by the same committee. Burden could be further reduced using a two-step process.

Two-step process

A two step process minimizes delays and review burdens for minimal risk projects while ensuring documentation of minimal review. The first step would involve submission of a succinct, e.g. one-page, document that summarizes key ethical considerations. A Alberta Canada Consensus Initiative has developed ethical criteria for consideration for QI projects. A children’s hospital in Australia has taken a similar approach to QI. These criteria, which are also relevant to QIR, include usefulness of knowledge, methods, fair appropriate selection of participants (or data), steps to maximize benefit and minimize risk, respect for rights of individuals, communities and populations, and informed consent. These criteria are similar to those used to determine IRB exemption.

The QI/QIR document would be reviewed by a person designated by the oversight committee (first step). This reviewer would either approve the project or refer the project for further committee review (second step). Optimally, this would be occur within a few days and not take longer than a week for a determination. This two-step process is similar to “expedited reviews.” Potential differences include a shorter application, shorter turn-around times, and review by members with QI/QIR ethics expertise.

Periodic auditing of documents and decisions by a second member of the oversight committee could help to standardize approval, referral decisions and documentation, while ensuring quality oversight through an audit trail. The first quick step minimizes the risk of projects being considered “exempt” from full review in the absence of auditable documentation of minimal, independent review.

Integration of Clinical and Research Ethics Oversight

Who should provide ethical oversight of QI/QIR? QI/QIR are sufficiently distinct from other types of clinical research that they warrant their own dedicated oversight committee. In theory, oversight committee could reside within an existing IRB structure, i.e. as an QI/QIR IRB committee. Alternatively and regulations permitting, it could represents a new organizational structure. Expertise on this oversight committee would
optimally include patients, including previous participants in QI/QIR, and experts in conducting QI and QIR, in addition to ethical oversight expertise. Improved integration of ethical oversight within the context of a learning health care system could be achieved by expanding committee membership beyond members with expertise in applying ethical principles to groups to members with expertise in applying ethical principles to individual patients. This could be accomplished by inviting members from Clinical Ethical Committees (CECs) to join the QI/QIR ethical oversight committee. CECs provide clinical consultations not only to clinicians, staff, patients, and families, but also establish and oversee institutional guidelines and procedures that involve ethical concerns. CECs are experienced in weighing risks and benefits during clinical care and thus could potentially offer a valuable perspective in applying ethical principles relevant to a learning health care system in the context of QI/QIR.

This integration of CECs into ethical oversight of QI/QIR would minimize the silos between research and treatment and facilitate cross-fertilization of expertise and perspectives. An integrated committee might provide more informed oversight of QI/QIR than IRBs with traditional membership.

Training of QI/QIR Ethical Oversight Committees

Even among traditional IRBs, there is wide variation in IRBs vary widely in their efficiency, perspectives, and requirements. Without doubt, members in an QI/QIR oversight committee will require training, ideally training that is provided conjointly with other members. Most patients have not been trained in ethical oversight, much less familiar with QI/QIR ethical issues. Many experts in QI have not been formally trained in ethical principles. Members of CECs will need to learn to apply ethical principles in the context of QI and QIR. Traditional IRB members will need to learn how to weigh protections to patients in the context of an imperative to continuously improve health care.

Training could include the purposes and methods of QI/QIR in addition to the potential benefits, risks, and burdens to the health care system (including patients, staff, clinicians and administration). Most notably, such training would include systematic means for balancing these competing risks in ways that facilitate rather than hinder the development of learning health systems, and provide a roadmap for integrating assessment, feedback, and review into the operations. This change in paradigm will not occur overnight. It will require an iterative process involving action, reflection, and revision. It will require careful attention to process over time including timeliness of reviews, useful revisions to projects, and input from multiple perspectives and stakeholders including patients. Most importantly, it will require openness to new
thinking, new ways for ethical review, and engagement of clinicians and patients in oversight.

Informed consent

Reluctance to subject QI to ethical oversight reflects a legitimate concern that such ethical oversight could undermine creation of learning health care systems. This includes concerns about problematic delays in implementing QI, but also concerns about the potential for requiring informed consent for participants in QI projects, and the likelihood of introducing selection bias by those who opt-in versus opt-out. These are valid concerns; there is an ethical obligation on the part of patients, staff, and clinicians to contribute towards a learning healthcare system, with benefits that accrue not only to the patients, but also to society as a whole.

Informed consent is intended to protect participants from exposure to additional risks posed by ‘research’ they have not agreed to beyond the standard of clinical care, while respecting their autonomy and preferences. This process is analogous to informed consent for patient care. In both cases, it balances benefits, risks and practical considerations. For example, informed consent is neither required nor routinely obtained for minimal-risk procedures, such as commonly ordered blood tests during patient care. Doing so could result in greater harm (through delays and wasted resources) than benefit. Formal informed patient consent is reserved for procedures where the stakes, both risks and benefits, are greater e.g. surgical procedures. A similar balance applies to QI and QIR.

Under current USA federal regulations, informed participant consent may be waived if the research in question poses “no more than minimal risk to the participants,” if failing to obtain informed consent “will not adversely affect the rights and welfare of the subject,” if “the research could not practicably be carried out,” and if “whenever appropriate, the subjects will be provided with additional pertinent information after participation.” These considerations are applicable to virtually all QI and much of QIR though the ultimate determination lies in the oversight committee assessment of competing risks and benefits. For example, it is not feasible to conduct a pragmatic trial of outreach for patients past due for cancer screening using traditional informed consent. The primary target population for these efforts would be systematically excluded by a requirement for informed consent because this population is the most difficult to reach due to change in address, phone numbers and infrequent office visits. Thus, results would not be generalizable to the population of interest. In this case, we agree with Faden et al that a waiver of informed consent is necessary.

Individual informed consent is often not feasible for cluster randomized controlled trials and comparative effectiveness research (CER) studies where the organization is the
primary target of the intervention.\textsuperscript{31,32} Requiring individual informed consent from all participants including all patients render these trials obsolete with accompanying loss of new knowledge. Obtaining waivers for individual informed consent in cluster randomized trials, requires consideration of feasibility, knowledge gained, and the balance of benefits and risks to participants.\textsuperscript{31,33,34}

Informing new patients upon their enrollment in care regarding potential QI/QIR and obtaining acknowledgement, i.e. universal consent, represents another way to inform patients when opt-out might not be feasible. This approach could strengthen requests for waivers of informed in the presence of favorable benefit-risk to participants while offering patients with the choice to obtain care at other organizations. For higher risk projects, opt-out approaches could be used to recruit (and subsequently consent) patients. This could include notifying patient by mail or electronically that a project has begun that they have the right to opt-out by calling a number.\textsuperscript{35} This passive approach to informed consent may minimize response bias that occurs with active, opt-in consent.\textsuperscript{36}

**SUMMARY**

QI and QIR are not reliably distinguishable. We recommend new approaches that build on existing structures, such as a two-step process, to facilitate ethical review of QI/QIR and promote learning health care systems within a rapidly changing health care environment. We recommend creating expert ethical oversight committees to review both QI and QIR. Such committees can operate under many existing regulations regarding minimal risk research and waivers of informed consent. The ultimate goal of this approach is to balance the protection of the rights of participants in QI/QIR with the ethical imperative to improve care as rapidly as possible by building a healthcare system that continuously learns from its data.

**Competing Interest:** The authors declare that they have no competing interests.

**Author’s contributions:** Authors jointly conceived of this work. K Fiscella wrote the first draft following discussions with the other authors. All authors contributed to revisions and approved the final manuscript.
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