The Keystone study of prevention of catheter-related infections in intensive care units raised important issues regarding infection control and research ethics. Infection control is an area common to public health and quality improvement. The performance of surveillance, the reporting of infection control data, and the response to complaints are all obligations raised by the international health regulations. The regulatory system around research ethics focuses on the individual subject in research and is not designed around areas such as infection control. Scientific methods are common to both infection control and research; both may result in “generalizable knowledge.” Infection control physicians should work with their institutional review boards to try to streamline the process of ethics review. Regulatory change may be desirable to define and limit what infection control activities are construed as research.

A recent publication by Pronovost et al [1] demonstrated the uncertain boundaries between research and quality improvement (QI). The Keystone study, which began in March 2004, was an evaluation of an accepted, evidence-based bundle of 5 interventions recommended by the Centers for Disease Control at the time [2] for the prevention of catheter-related bloodstream infections in a large number of intensive care units in Michigan. The bundle included compliance with hand hygiene, the use of full barrier precautions for line insertions, skin preparation using chlorhexidine gluconate, avoidance of cannulation of the femoral vein, and the removal of unused catheters, none of which was or is an intervention of significant known risk to patients. The impact of these measures was assessed over the subsequent 18 months. The results were dramatic, demonstrating a sustained 66% reduction in the rate of intravenous line–related sepsis. With the current US estimate of 80,000 cases of catheter-related bloodstream infection annually and with 28,000 of these cases being fatal [3], the implementation of the bundle could prevent 55,000 cases of catheter-related bloodstream infection and could save 18,000 lives and $2.5 billion dollars annually in the United States alone.

Despite these potential remarkable results, there was a firestorm around this study. An anonymous complaint was filed to the Office for Human Research Protections (OHRP) alleging that the study constituted research, that the rules of research were bypassed, that informed consent was not appropriately obtained from subjects, and that an applicable regulation (ie, Title 45 Code of Federal Regulations, Part 46, Protection of Human Subjects [45 CFR 46]) had not been followed. The protocol for the study had been submitted to the institutional review board (IRB) at Johns Hopkins University and was labeled as research by the applicant, and an exemption from IRB review was requested (under 45 CFR 46.101[b][5], study of public benefit or service programs); it was deemed exempt by the IRB (under 45 CFR 46.101[b][4], exemption based on the use of existing data, documents, records, pathological specimens, or diagnostic specimens). A lengthy debate ensued as to whether this study constituted research or QI [4, 5].

The present article examines the ethics of QI activities, including those related to infection control, from the vantage point of an outsider to the US system of research ethics. It seeks to conceptualize infection control activities as an area of overlap between QI and public health. In both QI and public health, there have been long discussions about what constitutes research and what constitutes routine and required activity. In both, there are investigations that are considered the expected activities designed to ensure or improve quality and health, and there are other investigations that are clearly related to research. In addition, there is a large grey area that is problematic to many observers. All of the organizations referred to in the present article are American, unless specifically referred to otherwise.
Research is defined by the Office of Human Subject Research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR 46.102[b]) [6]. It is a difficult definition for both QI and public health. In both, systematic, scientific methodology is used in routine activities, and the results are frequently generalizable.

The research ethics system focuses on individual rights in studies addressing individual study subjects. A human subject is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains either (1) [d]ata through intervention or interaction with the individual, or (2) [i]dentifiable private information" (45 CFR 46.102[f]) [6]. Research ethics reviews were not designed for QI or public health. Perhaps as a consequence, the research ethics system does not align perfectly with QI or public health, and stress points have appeared.

Federally funded research involving human subjects requires IRB review unless defined exemptions apply. These exemptions are clearly outlined in the regulations, and from the perspective of the OHRP, the delineation of what constitutes research is clear. From the ground, there is considerable uncertainty. The discussion surrounding the Keystone study is a prime example.

KEYSTONE STUDY: RESPONSE TO COMPLAINT

The OHRP, however, supported the complaint, calling the Keystone study nonexempt research conducted without adequate IRB review, and they demanded an IRB review at Johns Hopkins University as well as at each participating institution with a Federalwide Assurance for the protection of human subjects. A Federalwide Assurance reflects a process of registration of IRBs and the assurance of compliance by the OHRP with the regulations of the US Department of Health and Human Services, and it is necessary for research funded by the US Department of Health and Human Services. Furthermore, the OHRP claimed that Johns Hopkins University had failed to ensure that requirements for consent were followed. The Johns Hopkins University IRB instructed the principal investigator to put the study on hold until the study was in compliance. The study was suspended by the Michigan Health and Hospital Association at each institution until local IRB review was obtained and the need for consent addressed [4].

It must be noted that, in 2001, federally funded research at Johns Hopkins University had been suspended by the OHRP because of the death of a healthy volunteer in biomedical research, at great impact to the institution, perhaps sensitizing the university to OHRP interventions [7]. The university and the health and hospital association responded promptly to the issues raised in the Keystone study by the OHRP.

After the dust settled and the study resumed with IRB approvals, the OHRP noted that it would have been eligible for expedited review and waiver of consent requirements [8]. On the basis of the study results, further study of this bundle of interventions would no longer be construed as research.

PUBLIC REACTION

A lively national debate ensued regarding the ethics and regulation of the study, including postings on a major research ethics Listserve [9], articles in the New York Times [10 11] and the New Yorker [12], and communications from the OHRP. Dr. A. Gawande, a surgeon and investigator, stated that "the government’s decision was bizarre and dangerous" [11]. A more recent international study regarding the use of a surgical safety checklist, in which Dr. Gawande was an investigator, obtained ethics approval from his own institution as well as from the World Health Organization and each hospital involved; the requirement for consent was waived at each hospital [13].

Two commentaries in the New England Journal of Medicine presented differing views. Miller and Emanuel [4] thought that the study was research and that it required an IRB review. However, they thought that the study could have been reviewed in expedited fashion, that the informed consent requirement could have been waived, and that a single IRB review would have been sufficient for the study as a whole. They construed the purposes of the consent process as protection from risk and respect for autonomy. Here, informed consent was not practical, and no meaningful protection was lost in waiving it. Baily deemed the project "a combination of quality improvement and research on organizations, not human-subjects research" [5, p 769]. She saw no need for IRB review or for consent. She expressed concern that the IRB’s opinion differed substantively from that of the OHRP. Because “small changes in the facts of the situation can make a large difference in the regulatory burden imposed” [5, p 769], she called for a change in regulations.

Savel et al [14], in reviewing the Keystone study, highlighted the importance of QI research. They called for change from the OHRP and from healthcare institutions to support QI and streamline the approval process, and they suggested that small hospitals delegate to “regional centers of excellence” [14, p 727].

It seems that there was opportunity for differences of opinion among experts based on the sometimes nuanced arguments; there was, however, no nuance in the OHRP’s response to the initial complaint. In the OHRP’s opinion, due process had not been followed, and the study was suspended. In retrospect, other than the onerous requirement for IRB approval at each participating institution, the required solution would have been easily effected had it been clear to the investigators at the outset. Clearly, the favorable outcome of the study did not justify the waiver of IRB or consent rules. However, it made the position of the OHRP more difficult to defend in the public arena.
INFECTION CONTROL, PUBLIC HEALTH, AND QI

What have we learned from this case, and how do we move forward? We can start by reviewing the extensive discussions that have taken place regarding research ethics in the context of QI and in the context of public health. For example, we can construe infection control as an overlap area between QI and public health. Furthermore, recent legislative and regulatory changes regarding infection control mandate that health care institutions and governments implement surveillance programs and report certain infection rates. These changes only increase the similarity between infection control and public health. Finally, enormous importance is placed on the stringency of the protection of human subjects and on the stringency of the research that has provoked the outcry about the potential risks to individual rights. It is important that the IRB not pose a barrier, real or perceived, to legitimate and socially beneficial investigations that do not infringe on individual rights.

The Centers for Disease Control and Prevention focus on intent when defining what constitutes research [15]. They parse the definition of research and focus on the word “designed.” If the primary intent of a project is generalizable knowledge and not protection of the commonweal, then it is research.

Casarett et al [16] attempted to delineate what constitutes research in QI. They addressed the difficulties of using intent as a criterion, in that intent might be difficult to assess. Also, the results of QI activities may be generalizable and thereby might be caught up in the regulatory definition of research. They proposed a 2-step evaluation to construe an activity as research: that a majority of patients who were involved not be expected to benefit from the QI intervention or incur additional risks or burdens. They recognized the potential for increased workload for the IRB and investigators.

An expert panel convened by the Hastings Center defined QI as “systematic, data-guided activities designed to bring about immediate improvements in health care delivery in particular settings” [17, p 667] and construed it “an intrinsic part of good clinical care” [17, p 667]. The absence or paucity of QI activities is a sign of institutional dysfunction. QI is integral to the effective functioning of an institution and not an add-on. Failure to perform ongoing QI results in complacency and ignorance about the function of the institution and, inevitably, a decline in quality.

The Hastings Center asserted that there is an obligation for patients to allow their data to be part of institutional QI, provided there is no incremental risk or discomfort to the patients. There is a corresponding obligation of the institution and its agents to ensure patient privacy and confidentiality. If there is risk or discomfort involved, then participation must be voluntary. Often, health care workers are subjects, intentionally or inadvertently, in QI activities. Risks of divulging incompetency or redundancy are not sufficient to make participation voluntary, but risks beyond the normal work situation require informed consent. For example, it is reasonable to track rates of surgical site infections by surgeon as part of an infection control program without consent. This might identify a sloppy surgeon, and there might be consequences to the surgeon. As such, there is a difference between the research setting and QI in terms of voluntariness.

The Hastings Center focuses on local QI initiatives and implies that there should be concern about potential bias in measured outcomes if a subset of potential participants chooses not to participate. The Center assumes a direct potential benefit to the patient group if not to the individual participant. A small local assessment of administrative function or adherence to a generally accepted standard can be conveniently lumped into the designation of QI. Can QI be extended over a large purview—a region, state, country? There is no reason to believe why it could not be.

Public health surveillance activities have always been mandated by legislation, at the national or state level. The draft second edition of the Tri-Council Policy Statement states that “public health surveillance that is legally mandated” is exempt from ethics review [18, p 18]. There has long been legal and ethical obligations on the part of public health authorities to engage in surveillance and infection control activities to satisfy this mandate. In the past, a major distinction between public health and infection control was the absence of legislation governing infection control. It would appear that the law is changing and that the restrictive traditional view of what constitutes public health activity is no longer adequate. Infection control was informally delegated as serving as the agent of local public health authorities in the hospital. This distinction began to change in the past few years. The International Health Regulations [19] were revised in 2005 and took effect as international law on 15 June 2007. The scope of the International Health Regulations broadened to include “public health emergencies of international concern” [19, p 15], and member states were obligated to increase infection surveillance and reporting. It is less clear what infections fit this criteria. The following types of pathogens would presumably be included: a multidrug-resistant virulent pathogen such as methicillin-resistant *Staphylococcus aureus*, a novel serotype of influenza virus such as H1N1 (representing antigenic shift), or a virulent organism such as the NAP1/027 strain of *Clostridium difficile*. Hospital infection control activities constitute the primary surveillance for these organisms. The vagueness of terminology in the International Health Regulations blurs the distinction between hospital infection control activities and traditional public health. Wilson et al [20] argue that there is an obligation on the part of health care institutions to engage in ongoing surveillance and infection control activities, and that there is a
corresponding obligation on the part of governments to support these activities. Infection prevention and control then differs from other QI activities in the hospital in terms of being legally mandated.

A number of local jurisdictions have enacted legislation with regard to surveillance and the reporting of infection control data. In the United States, 38 states have legislation in progress regarding healthcare-associated infections. Of these 38 states, 26 mandate public reporting of infection rates [21]. In Canada, Ontario has recently enacted obligatory public reporting of rates of infection due to vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, and *C. difficile*; as of April 2009, surgical site infections, ventilator-associated pneumonia, and central line infections are to be reportable as well [22]. There has been enormous public interest. Also, hospital accreditation in Canada demands evidence of infection control activities, with specific indicators including rates of either methicillin-resistant *S. aureus* or *C. difficile* infection, as well rates of surgical site infection and the “rate of timely administration of prophylactic antibiotic” [23]. Surveillance of personal health information is no longer a voluntary activity of well-meaning institutions. It is the obligation of hospitals to maintain accreditation status, and it is a legal requirement at the provincial, state, national, and international level. How this plays out in a federation such as the United States or Canada has been the object of debate and concern in Canada. The Auditor General of Canada recently published a third report about the state of public health in Canada, criticizing the Public Health Agency of Canada for inadequate surveillance and reporting [24]. There is an expectation of surveillance for infectious diseases. Infection control is an obligatory standard of practice.

Numerous studies have described the IRB process as providing a barrier to the conduct of multicenter studies, with inconsistent reviews, a process leading to excessive complexity of consent documents, and huge resource implications all resulting in large and undue delay in initiation of studies [25]. From the IRB perspective, the IRB is flooded with work such that it is difficult to give due time and attention to reviews. It would seem reasonable for the IRB to restrict its attention to what it must do, to what it does usefully in terms of human subject protections, and to avoid “mission creep.” The goal should not be simply regulatory compliance; regulation that fails to protect and only serves to delay (by increasing costs and complexity) must be reassessed. The IRB should not be involved unnecessarily in infection control studies that pose no risk to the well-being of patients.

Fost and Levine [26] expressed concern about the IRB system becoming too bound up in regulations, with an unduly strict and narrow interpretation and attention to minutiae, a punitive approach from regulators, timid institutional administrators with insufficient knowledge of IRBs, an overzealous approach to research ethics to avoid regulatory noncompliance, and accreditation agencies that rigidly enforce the system. We must listen to these critiques.

There is no agreement as to the adequacy of current regulation regarding research ethics in the United States in terms of infection control; in Canada, the draft second edition of the Tri-Council Policy Statement does not directly address infection control and only alludes to QI activities as outside the realm of research ethics [18]. A number of years ago, the National Bioethics Advisory Committee in the United States proposed limitations on the oversight of IRBs with regard to infection control [27]. They proposed a redefinition of the term “research” to exclude “high-benefit, low-risk activities such as public health surveillance and some forms of quality improvement” [27, p 497]. Perhaps, as the political pendulum swings, this proposal can be revisited.

What does the infection control investigator do? There are 2 related issues: (1) delineation of what constitutes research and (2) the burdensome nature of individual institutional reviews of large multicenter trials. Both relate to a research ethics review system that risks suffocating minimal-risk research and QI. The consequences to institutions of a wrong adjudication—incalling for an investigation of quality assurance—may be profound, and there is the obvious temptation for risk avoidance and for treating as research all activities that can possibly be construed as research.

Institutions must have timely access to the OHRP for opinions regarding individual studies. Regulations call for the proportionality of the IRB review, with minimal-risk studies having less stringent demands. Although there are dissenters who believe in the inherent difficulty of assessing risk in studies and in the need for full board review [28], risk in infection control studies is typically minimal, is readily assessed by moderately knowledgeable individuals, and varies little from study to study. If there is to be proportionality of the IRB review, then the consequences of taking the research route must not be draconian or unduly burdensome. Institutions must have well-functioning, expedited review mechanisms and must be familiar with IRB regulation. Conversely, if the work is deemed not to be research, then there should be clear standards for respecting the privacy and well-being of the patients involved.

Investigators should expect to work out these issues with their IRBs. Investigators who collaborate frequently can explore whether their IRBs can be similarly coordinated to streamline the process of ethics review.

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References


