Quality Improvement or Research? Implications of OHRP’s Response to the Keystone: ICU Project

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In October 2003, the Michigan Health and Hospital Association (MHA), in collaboration with Johns Hopkins University (JHU), launched the Keystone: ICU project with a matching grant from the federal Agency for Healthcare Research and Quality (AHRQ). Currently more than 100 hospitals participate in developing and implementing interventions to improve the quality and safety of healthcare services provided in hospital intensive care units (ICUs). The typical implementation team at a given ICU includes a senior hospital executive, ICU physicians, nurses, and administrators, and others. Each team commits to attend biannual meetings, participate in conference calls, implement specified interventions, and share results. MHA provides important management and support services; and Blue Cross and Blue Shield of Michigan (BCBSM) grants incentives totaling millions of dollars to hospitals that achieve specified quality and safety thresholds. MHA calculates that, between March 2004 and March 2007, the initiative resulted in more than 1,700 patient lives saved, reduction of more than 100,000 hospital days, and a total cost savings of nearly $250 million.

The Department of Health and Human Service’s Office for Human Research Protections (OHRP), which enforces the Common Rule, received a complaint about the project following publication of results of a successful initiative to reduce bloodstream infections and, consistent with its standard practice, launched an inquiry. On July 19, 2007, the agency issued a “Determination Letter” to JHU. The letter faulted JHU for conducting non-exempt human subjects research without Institutional Review Board (IRB) approval and without informed consent, and rejected JHU’s arguments that the project was not subject to regulation. Although the lay media and academics around the country later criticized OHRP’s findings—and initial directive to suspend the activities and refrain from publishing resulting data—as an example of bureaucratic over-reach, the facts presented to OHRP in the original complaint and subsequent analysis, together with the literal language of the Common Rule as it exists today, arguably left the agency with little room to maneuver. Among other challenges identified by OHRP:

- JHU project leads had described the project as research involving human subjects in their AHRQ grant application;
- The project involved “testing” an intervention in the ICU setting—not just the collection or study of data, documents, or records;
- The data, documents, and records that were collected and studied did not exist until after the research was proposed to JHU’s IRB;
- The clear intent of the project was to study/test several hypotheses regarding the efficacy of the proposed interventions; and
- JHU’s contention that even if it was “human subjects research,” the project was “exempt” from IRB review under 45 C.F.R. § 46.101(b)(4) was unsupported because the project involved prospective collection and analysis of identifiable data.

OHRP specifically opined that, under the Common Rule, “quality improvement activities can also be research activities” and concluded, notwithstanding JHU’s arguments to the contrary, that JHU, MHA, and most of the involved hospitals had engaged in non-exempt human subjects research without appropriate IRB oversight or informed consent.

In November of last year, OHRP issued a follow-up letter to JHU and a separate letter to MHA reiterating the agency’s position. In the JHU letter, OHRP criticized a new JHU policy created in response to the original determination letter. The policy provided that: “When the purpose of an activity is to assess the success of an established program in achieving its objectives and the information gained from the evaluation will be used to provide feedback to improve that program, the activity is not human subjects research.” OHRP made clear its position that no such sweeping generalization can be made.

The agency’s enforcement activities eventually came to the attention of the lay media, most notably surgeon and popular commentator Atul Gawande. Gawande published an article in The New Yorker and an op-ed piece in The New York Times describing the astonishingly positive results of the project and accusing OHRP of jeopardizing critically important quality improvement work in favor of rigid adherence to a regulatory regime that is ill-suited to quality improvement practice. The Gawande pieces focused national attention on the difficulties faced by JHU and other institutions and their IRBs in navigating a complex set of regulations originally developed and arguably better suited for interventional biomedical research. And while OHRP eventually permitted the intervention to go forward as a
“non-research” activity, substantial confusion remains throughout the industry about how to handle similar initiatives.

This article summarizes the relevant regulations, identifies the challenges faced by institutions when reviewing quality improvement (QI) projects, and provides guidance on issues institutions and their IRBs should be counseled to consider in analyzing individual cases.

What is Human Subjects Research and When is it Regulated by an IRB?

Seventeen federal agencies and offices have adopted a single policy for the protection of human participants in research, known as the “Common Rule.” OHRP enforces the Common Rule in research supported by the U.S. Department of Health and Human Services. The Common Rule requires institutions engaged in federally supported human research to assure that the activity is conducted ethically and consistent with federal regulations. It imposes obligations on researchers to secure advance IRB approval and continuous oversight for most research projects, and to secure from prospective subjects written informed consent unless an IRB grants a waiver.

The Common Rule defines “research” as a “systematic investigation . . . designed to develop or contribute to generalizable knowledge” and a human subject as “a living individual about whom an investigator . . . conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.” Examples of interventions include physical procedures performed to collect data (such as blood draws or imaging studies), and “manipulations of the subject or the subject’s environment that are performed for research purposes.” An interaction is a communication or contact between an investigator and a subject, for example via administration of a survey.

Only research involving human subjects is regulated by the Common Rule and, thus, subject to IRB oversight. An IRB becomes involved at any given site only when that particular site is “engaged” in the research. Guidance issued by OHRP in 1999, 2004, 2006, and 2008 (collectively the Engagement Guidance) defines circumstances where a healthcare provider may furnish researchers with data without itself becoming engaged in their research.

Why is There Confusion—and What’s the Big Deal?

While the definition seems simple enough on first read, clear-cut, objective distinctions between “research” and “practice” have long eluded researchers, healthcare providers, and public health practitioners. Yet the implications of a finding that a given project constitutes research, and not quality improvement, for example, can be significant. They include:

- A requirement to secure IRB approval (or exemption) and oversight;
- Annual IRB review unless an exemption is granted;
- Informed consent (or waiver of consent) to participate in the study, required under the Common Rule for non-exempt research; and
- Authorization (or waiver of authorization) for use of health information, required under the Health Insurance Portability and Accountability Act of 1996 and associated privacy and security regulations (collectively HIPAA), unless the purpose of the project is primarily QI.

These activities are perceived to be time-consuming and costly (and often are). More important, compliance with consent and authorization requirements found in the Common Rule and in HIPAA, respectively, can result in statistically significant bias in research results related to characteristics such as age, geographic location, and nature of injury or illness.

How Can I Tell the Difference?

For these reasons, many individuals and organizations have sought to identify objective distinctions between research and practice. In 1999, for example, the Centers for Disease Control and Prevention published Guidelines for Defining Public Health Research and Public Health Non-Research. CTIC’s approach, unfortunately, relies in part on a primary purpose test (i.e., a project that is primarily undertaken for public-health, rather than research purposes, is public health, not both) that arguably is inconsistent with the definitions of “research” and “human subject” in the Common Rule and that OHRP explicitly rejected in the Keystone case.
The reality, though, is that currently there is no clear distinction between QI and research. The best QI projects begin with a hypothesis that an evidence-based change in practice will improve care, adopt that change systematically, measure outcomes, and make adjustments based on the resulting analyses. In some cases, the information developed during project implementation and evaluation is so important that project leaders want to share it with others by publishing results. This “plan-do-check-act” process sounds a lot like the scientific method. It is no surprise, then, that the two are easily confused.

Responding to these challenges, and to a chorus of demands in the medical community to accord QI projects special treatment, regardless of regulatory directives and sometimes blind to ethical problems that might result, a bioethics think tank called The Hastings Center published a comprehensive report in 2006 titled Ethics of Using QI Methods to Improve Health Care Quality and Safety. The authors defined QI to include:

systematic, data-guided activities designed to bring about immediate, positive changes in the delivery of health care in particular settings. While QI uses a wide variety of methods, they all involve deliberate actions to improve care, guided by data reflecting the effects. Depending on the activity, QI can look like a type of practical problem solving, an evidence-based management style, or the application of a theory-driven science of how to bring about system change. Introducing QI methods often means encouraging people in the clinical care setting to use their daily experience to identify promising ways to improve care, implement changes on a small scale, collect data on the effects of those changes, and assess the results. The goal is to find interventions that work well, implement them more broadly, and thereby improve clinical practice. Alternatively, a QI activity might begin with a review of aggregate data at the patient, provider, clinical unit, or organizational level to identify a clinical or management change that can be expected to improve care. The change is made, the effects are monitored, and conclusions are drawn about whether the change should be made permanent. QI can also mean collecting data from multiple organizations, analyzing it to understand what drives positive change, and using the results to design and implement a strategy to achieve a specific improvement across organizations. At its heart, QI is a form of experiential learning and discovery.

The report nicely illustrates the complexities of any research/QI analysis and demonstrates convincingly that no single objective test or standard can make the task easy. The report does, though, identify the characteristics of a project that tend to favor a finding that the project includes both QI and research and, therefore, should be reviewed by an IRB (and, in the authors’ view, ideally a specialized QI IRB).

Counsel can use the analysis to aid their clients in distinguishing between QI and research by asking the following questions:

1. Are patients randomized into different intervention groups in order to enhance confidence in differences that might be obscured by nonrandom selection? Randomization done to achieve equitable allocation of a scarce resource need not be considered.

2. Does the project seek to test issues that are beyond current science and experience, such as new treatments (i.e., is there much controversy about whether the intervention will be beneficial to actual patients)—or is it designed simply to move existing evidence into practice? If the protocol is performed to implement existing knowledge to improve care—rather than to develop new knowledge—answer “no.” Note that the “intervention” in question might be a patient intervention such as a new drug or procedure, or an educational intervention directed to physicians or other caregivers.

3. Are researchers who have no ongoing commitment to improvement of the local care situation (and who may well have conflicts of interest with the patients involved) involved in key project roles? Generally answer “yes” even if others on the team do have professional commitments. However, where the project leaders with no clinical commitment are unaffiliated with the project site, it may be that the project site is not engaged—and does not require IRB approval/oversight—even if the project leaders’ roles do require IRB oversight at their institutions.

4. Is the protocol fixed with a fixed goal, methodology, population, and time period? If frequent adjustments are made in the intervention, the measurement, and even the goal over time as experience accumulates, the answer is more likely “no.”

5. Will there be delayed or ineffective feedback of data from monitoring the implementation of changes? Answer “yes” especially if feedback is delayed or altered in order to avoid biasing the interpretation of data.

6. Is the project funded by an outside organization with a commercial interest in the use of the results? Is the sponsor a manufacturer with an interest in the outcome of the project relevant to its products? Is it a nonprofit foundation that typically funds research, or internal research accounts? If the project is funded by third-party payors through clinical reimbursement incentives, or through internal clinical/operations funds vs. research funds, the answer to this question is more likely to be “no.”
7. If the project involves randomization for confidence or testing of new or controversial interventions, it is likely research requiring IRB oversight. Otherwise, if the weight of the remaining answers tends toward “yes,” the project typically should be considered “research” and approved by an IRB prior to implementation. If the weight of the answers tends toward “no,” the project reasonably may be considered “not human subjects research” or subject to IRB oversight. While arguably somewhat subjective, the above considerations provide a reasonable framework for institutional policies that could likely withstand OHRP scrutiny. They are also consistent with OHRP’s eventual decision—on Valentine’s Day this year—to recognize the Keystone ICU project, at least in its current form, as practice and not research. It is true that some institutions or IRBs might cite OHRP’s concern, expressed in the original JHU Determination Letter, that the project was developed to test by hypotheses and that it involved an intervention, in support of more conservative policies that are likely to trigger IRB oversight of a broad range of QI activities. Where this occurs, researchers and IRB members can, at a minimum, take advantage of the flexibility the Common Rule provides to minimize unnecessary burden on or interference with the research activity.

Summary

Many projects initiated primarily for QI purposes are also “human subjects research” as defined in the Common Rule. Yet unlike the HIPAA privacy rule, the Common Rule recognizes no “primary purpose” test. Nevertheless, counsel can undertake a relatively simple analysis to assist their clients in differentiating between QI and research activities when such a distinction can be made, and to minimize administrative burden consistent with ethical research practice when one cannot.

Practice Tips

• Develop a local institutional policy that not only defines, consistent with the Common Rule and Food and Drug Administration regulations, what is human subjects research, but also defines quality improvement, program evaluation, and other activities that may not be research.

• Train IRB members and staff, researchers, and QI professionals to understand the difference between research and QI and the circumstances where a project may qualify as both.

• Develop a decision support tool for project leaders and/or IRB members and staff using the Hastings Center criteria or others that can withstand regulatory scrutiny.


6 The February 21, 2008, NEW ENGLAND MED. published two perspective pieces, one of which was similarly critical. The second, co-authored by Ezekiel Emanuel, Chair of the Department of Bioethics at NIH, concluded that the project was subject to IRB oversight (from the coordinating institution, not at each individual participant institution), but did not require informed consent of individual subjects.


8 See, e.g., 45 C.F.R. § 46.106(c).

9 Institutions may agree to voluntarily comply with the Common Rule even for non-federally supported research. See www.hhs.gov/ohrp/human_subjects_assurance/assurance.html. Those that are accredited by the Association for the Accreditation of Human Research Protection Programs adhere to standards that do not vary by funding source.

10 45 C.F.R. § 46.102(d) (emphasis added).

11 45 C.F.R. § 46.102(f).


14 Office for Human Research Protections, DRAFT: OHRP Guidance on Engagement of Institutions in Human Subjects Research (Dec. 8, 2006), available at www.hhs.gov/ohrp/draft/engagement.htm. The final draft update to the 1000 guidance referenced above is not yet final, but has been referenced by individual OHRP staff in public meetings and private conversations as representative of their current thinking on the subject.

15 See, e.g., L. Joseph Melton, 337 NEW. ENG. J. MED. 1466-1470 (Nov. 13, 1997); Steven H. Woolf, et al., Selection Bias from Requiring Patients to Give Consent to Examine Data for Health Services Research, 1 ARCH. FAM. MED. 1111-1118 (Nov. 2000).

16 The guidelines are available at: www.cdc.gov/od/ocsce/research_definition.htm; see also Virginia Immanuel, Karin Johnson, Barbara Young, Gene Hart, Testimony on Secondary Uses of Health Data to the National Committee on Vital and Health Statistics (July 31, 2007).

17 Some have argued a distinction between human research, on one hand, and organizational research, on the other. See, e.g., Mary Ann Baily, Norming Through Protection?, 358 NEW. ENG. J. MED. 768 (Feb. 21, 2008). However, the regulations really do not support such an analysis. If the project is “research,” and the research requires collection of identifiable private information, then it is human subjects research; if it is federally supported, then it is subject to the Common Rule.


19 The letters recognizing this position are posted at www.hhs.gov/ohrp/determination_letters/YR08feb08b.pdf (MLA) and www.hhs.gov/ohrp/determination_letters/YR08feb08b.pdf (JHU). In brief, OHRP determined that the research project had occurred from 2003-2005 and that, by 2007, when the agency first learned of the project, the participating hospitals had in fact operationalized the program and were no longer conducting research involving human subjects.

20 See, e.g., Franklin C. Miller and Ezekiel J. Emanuel, Quality Improvement Research and Informed Consent, 358 NEW. ENG. J. MED. 765 (Feb. 21, 2008); infra note 6. For multi-institutional studies, institutions can rely on 45 C.F.R. § 46.114 to avoid duplicative review but in those cases where the studies are federally supported or the institutions are subject to the Common Rule regardless of funding source, those “deferring” review must enter into IRB authorization agreements and list the responsible IRB on their federal-wide assurances.

21 45 C.F.R. § 164.501.