Innovation in Clinical Research Regulation

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Innovation in research encompasses new questions, drugs, devices, and protocols, but also new research methods and regulations. Whereas innovative new results receive most of the investigator and public attention, innovation in research regulation is critical to enabling and facilitating research conduct, and to reducing research cost, increasing efficiency, and ensuring the rights and protections of those patients and volunteers on which research depends, and for whose eventual benefit research is conducted.

This issue of Anesthesiology contains two articles that illustrate innovative and flexible approaches in research regulation.[1,2] One article is an Original Investigation which reports a clinical study of two methods for assessment of patient frailty and their performance in predicting hospitalization and serious complications after surgery.[1] The study was performed using a waiver of written informed consent of the research subjects, which was done with the approval of the hospital's institutional review board. Investigators provided each patient, ahead of surgery, a patient information sheet with details of the study. Verbal consent for inclusion in the study was obtained by the anesthesia provider during the preoperative visit, and patients were given the opportunity to opt out if they desired to do so. A more traditional and expansive written informed consent document, signed by both patient and investigator, was not required. The second article is a Special Article that addresses the alteration or waiver of consent for minimal risk comparative effectiveness trials.[2] It presents perspectives and approaches in three different countries. These two articles illustrate innovative and flexible approaches to clinical research and the consent and protections of human research participants.

"The overarching issue is the importance for institutional review boards to evaluate critically how best to allow individuals to make decisions regarding research participation, and to facilitate a research process that is least burdensome to both the participant and the researcher."

Human subjects research regulation in the United States falls under the jurisdiction of the federal government and is codified in a statute called the Federal Policy for the Protection of Human Subjects (45 CFR part 46 or the "Common Rule"). Major changes were also made in the Common Rule in 2018, so there are pre-2018 and post-2018 (revised Common Rule) requirements. Human research is somewhat of an anomaly in federal regulation, which is typically very detailed and proscriptive. In contrast, federal regulations broadly charge institutional review boards with the protection of human research subjects but give institutional review boards wide discretion and flexibility to implement the broad regulations. Different institutional review boards may assess the same research protocol differently, require different protocol modifications, or require different language in an informed consent document. In addition, the Common Rule applies only to studies conducted by or funded by one of the signatory federal agencies, and institutions have the option of applying it only there, or to all research. For nonfederally-funded studies, organizations have greater latitude in defining equivalent protections and therefore much greater flexibility in their approaches. Conversely, other federal agencies (*e.g.*, Food and Drug Administration) may have different regulations in addition to or instead of the Common Rule which may limit this flexibility. Institutional review boards may also be affected by the process of voluntary certification by organizations such as the Association for the Accreditation of Human Research Protection Programs, Inc. (colloquially, AAHRPP).

Image: J. P. Rathmell.

This editorial accompanies the articles on pp. 44 and 82.

Accepted for publication September 9, 2019. From the Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina.

 Anesthesiology 2020; 132:1–4. DOI: 10.1097/ALN.0000000000003026

<zdoi;. DOI: 10.1097/ALN.0000000000003026>

Some institutional review boards may view regulations as directive (requiring only what is stated; a more minimalist approach), whereas others may view them as the bare minimum upon which to build additional regulatory superstructures and requirements (a more maximalist approach). Various factors may influence an institution's approach, including previous institutional experience, public or private organization, general counsel (private institution) or attorney general (public universities) and their legal perspectives, risk managers, senior institutional leadership, and sovereign immunity or endowment at risk. In addition, different institutional review boards may view their roles as managing risk or preventing uncertainty. Risk addresses known potential outcomes, with assigned probabilities, and can be measured, quantified, controlled, and communicated to potential research participants. Importantly, it can be managed and minimized. Uncertainty involves unknown future events, whose probabilities are also unknown, and cannot be measured, quantified, controlled, minimized, managed, or communicated to potential research participants. Innovative institutional review boards focus on helping investigators define, manage, minimize, and communicate risk, so that research subjects can make informed decisions. Other institutional review boards may focus on trying to prevent uncertainty. Uncertainly is not preventable.

One major advantage to the flexibility in federal regulations is that it permits institutional review boards to take innovative approaches to implementing the regulations. Such flexibility can not only reduce regulatory burdens but can also improve subject protections and allow for research types not existing or envisioned when regulations were written (*e.g.*, scale and nature of information collected, new procedures, new research settings, new topics, and even new disciplines).

The focus of both articles in this issue is comparative effectiveness research. This is defined as "the conduct and synthesis of research comparing the benefits and harms of various interventions and strategies for preventing, diagnosing, treating, and monitoring health conditions in real-world settings."[3] It aims to improve health outcomes by developing and disseminating, to patients and clinicians, evidence-based information about which interventions are most effective, and accelerating that awareness. Two key elements embedded in this definition are (1) the direct comparison of interventions known to be effective, and (2) their study in patients who are typical of day-to-day clinical care. Whereas many clinical trials compare an investigational drug or device with a placebo, randomized clinical trials in a comparative effectiveness domain have least two active (nonplacebo) interventions, which are already in clinical use. Placebo-controlled trials may ask "does this new thing work?" whereas comparative effectiveness research asks, "of what we currently do, which works better practically?"

Comparative effectiveness research has less formal regulation than other forms of research, and institutional review boards have more interpretive flexibility. It also presents interesting challenges for institutional review boards because it is governed by the regulations yet there is no federal regulatory guidance about interpreting and applying the federal regulations to this relatively new and rapidly growing area. Some institutional review boards may view comparative effectiveness studies as being "research involving no more than minimal risk to human subjects." Minimal risk is a statutory term, "meaning that the probability and magnitude of physical or psychologic harm anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychologic examinations or tests" (45 CFR § 46.102[j]). Nevertheless, there is ambiguity and conundrum in this definition.[4] Is the minimal risk standard one of absolute risk (that of daily life of an everyday person in the general population) or of relative risk (compared with the population being studied—*e.g.*, surgical patients)? And if the former, whose daily life? Bioethicists and investigators still argue this question, and different institutional review boards may apply different minimal risk definitions. And, what we as clinicians think of as minimal risk, what institutional review boards perceive, and what regulations define, may be very different. Arguably, the relative risk definition allows for a more innovative and flexible approach to conducting comparative effectiveness research. The concept of "minimal risk" is at the heart of many important regulatory determinations and requirements (such as waiver of consent, and waiver of documentation of consent). More research will be deemed "minimal risk" under the relative *versus* absolute minimal risk definition, meaning that more flexibility is available for regulatory oversight. Thus, the key area of flexibility for comparative effectiveness research is how the definition of "minimal risk" is interpreted and applied.

The study reported by Sonny *et al.*,[1] and approved by the Cleveland Clinic institutional review board, made maximal use of regulatory flexibility to reduce the work of the study team and thereby maximize efficiency. That is, participants were not required to sign a research consent form (waiver of documentation, per 45 CFR § 46.117). How was this done? The institutional review board deemed the study to be minimal risk and therefore qualified for a regulatory waiver of documentation of consent, combined with a patient information sheet distributed in advance describing details of the study, and then verbal consent was obtained by the provider during the preoperative visit. It is important to distinguish between the regulatory concepts of waiver of documentation of consent (*i.e.*, signing a consent form) and waiver of consent (*i.e.*, obtaining prospective agreement to participate). This is a common misunderstanding. Sonny *et al.* did obtain patient consent, but it was verbal (and presumably then documented by the investigators). The pertinent issues are consent for patient participation in the research and for investigator access to medical records. The

institutional review board waived the requirement for written consent and signature in favor of just verbal consent, because they deemed the risk as minimal. Consent applies to both medical records access and patient participation.

How else might the institutional review board have required the research to be conducted? The institutional review board could have required subjects to read and sign a consent form for all study procedures, including extracting information from medical records. This is the most conservative approach and might have been required at other institutions. And it requires the most work from researchers and the most time from participants. Some might posit that requiring subjects to read a lengthy consent form might actually interfere with true comprehension of the research. With regard to just investigator access to medical records, the institutional review board could have required signed written consent. Other institutional review boards might have, particularly because the participants were already in the preoperative clinic and therefore available to do this. The institutional review board could also have required a written signed consent form but waived some of the required elements (*e.g.*, describing an alternative to participation). The institutional review board could also have, if it believed that circumstances made it "not practicable" to obtain any consent for the research, granted a total waiver of all consent. The institutional review board chose a middle ground, more innovative than the most conservative of potential approaches, but still requiring patient consent. Another innovative aspect, not required by regulation, was the institutional review board requirement for the patient information sheet. That is laudable from an ethical and patient comprehension perspective, but it may also have increased the likelihood that participants would agree to participation during the verbal consenting process, and it may also have simplified that process.

The Special Article by Symons *et al.*[2] presents a more complex thesis because it addresses pragmatic clinical effectiveness research, where there is randomization between interventions (albeit all are standard of care), and the differing regulatory and ethical landscapes across countries, illustrated for the United States, England, and Australia. Specifically, the article asks whether international ethical guidelines and the policy frameworks permit altered or waived consent for nonemergency minimal-risk pragmatic trials. It highlights the inherent tension between continuous, cost-efficient, pragmatic clinical research to incrementally inform and improve care, and the inalienable need to protect patients, often conflated with the signing of a written consent document. Symons *et al.* provide international ethical guidelines, regulatory constructs, and ethics committee perspectives, using three research examples. The article also presents the challenges of variability (across countries, and the impact on international trials) and uncertainty (how to plan multiyear trials, years in advance, not knowing what future regulations will require). Readers are commended to this article because they may plan and lead clinical studies, participate in them as caregivers, and read the results, and, even if not for this, be challenged by the framework presented. If this article is both educational and stimulates discussion and debate (it did among the Journal's peer reviewers), the field and Anesthesiology will be much the better.

Clinical investigators know that informed consent documents have become longer, more complicated, and perhaps actually less informative. As noted, "Consent forms are increasingly long and complicated, obscuring important details, and are often designed to serve the interests of institutions and sponsors, and participants often have a limited understanding of study information even when they have signed a consent form."[5] For minimal risk comparative effectiveness research, a short and focused patient information sheet may actually be more informative, and provide a more informed consent, than an exhaustive and a complicated multipage treatise.

Clinical trials are undergoing substantial evolution and innovation, with the creation and implementation of novel trial designs. These include, for example, adaptive designs,[6] pragmatic trials,[7,8] cluster randomization,[9] comparative effectiveness research, and point-of-care trials.[10] In the United States, then Food and Drug Administration Commissioner Scott Gottlieb noted, in announcing a new pilot program to advance innovative clinical trial designs and make them more modern, effective, and efficient: "The aim is to develop more efficient strategies to assess the safety and efficacy of medical products earlier in the development process and to adopt innovative techniques that help make clinical trials more cost efficient and flexible, enabling innovators to advance new approaches to care" (https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm618829.htm; accessed August 1, 2019). Both human subject regulations and their implementation must evolve and innovate in tandem with research innovations, creating a supportive policy environment, for these aims and novel designs to be realized. Former Commissioner Gottlieb described the new trials design program as an "idea incubator." A similar idea incubator in the human subject regulatory sphere would be important and welcome. Indeed, this is happening. The existence of the Secretary's Advisory Committee on Human Research Protections (SACHRP, https://www.hhs.gov/ohrp/sachrp-committee/index.html; accessed August 1, 2019), the AEREO Consortium to Advance Effective Research Ethics Oversight (https://www.med.upenn.edu/aereo/; accessed August 1, 2019), and the Flexibility Coalition (https://oprs.usc.edu/about/initiatives/flexibility-coalition/; accessed August 1, 2019) should offer optimism about potential improvements in research regulation and institutional review board reviews.

The specialty of anesthesia has previously been innovative in clinical research implementation and human subjects protections.[11] For example, obtaining consent for research participation in clinical trials on the day of surgery, rather

than traditionally mandated consent before the day of surgery, vastly improves operational efficiencies, but did not affect the ethical elements of consent, patient anxiety, or obligation to participate or cause regrets about participation.[12,13] The overarching issue is the importance for institutional review boards to evaluate critically how best to allow individuals to make decisions regarding research participation, and to facilitate a research process that is least burdensome to both the participant and the researcher. The articles in this edition of Anesthesiology illustrate continued efforts in innovating clinical research and clinical research regulation, while still protecting human research participants.

Research Support

Support for this work was provided by the National Institutes of Health (Bethesda, Maryland; grant No. R01 DA042985).

Competing Interests

Dr. Kharasch is the Editor-in-Chief of Anesthesiology and his institution receives salary support from the American Society of Anesthesiologists (Schaumburg, Illinois) for this position.

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References

1. Sonny A, Kurz A, Skolaris LA, Boehm L, Reynolds A, Cummings KC III, Makarova N, Yang D, Sessler DI: Deficit accumulation and phenotype assessments of frailty both poorly predict duration-of-hospitalization and serious complications after noncardiac surgery. Anesthesiology 2020; 132:82–94
2. Symons TJ, Zeps N, Myles PS, Morris JM, Sessler DI: International policy frameworks for consent in minimal-risk pragmatic trials. Anesthesiology 2020; 132:44–54
3. Conway PH, Clancy C: Comparative-effectiveness research–implications of the Federal Coordinating Council's report. N Engl J Med 2009; 361:328–30
4. National Research Council: Proposed revisions to the common rule for the protection of human subjects in the behavioral and social sciences. Committee on revisions to the common rule for the protection of human subjects in research in the behavioral and social sciences. Board on behavioral, cognitive, and sensory sciences, committee on national statistics, division of behavioral and social sciences and education. Washington, DC, The National Academies Press, 2014
5. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G: Informed consent. N Engl J Med 2017; 376:856–67
6. Chow SC: Adaptive clinical trial design. Annu Rev Med 2014; 65:405–15
7. Califf RM, Sugarman J: Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015; 12:436–41
8. Simon KC, Tideman S, Hillman L, Lai R, Jathar R, Ji Y, Bergman-Bock S, Castle J, Franada T, Freedom T, Marcus R, Mark A, Meyers S, Rubin S, Semenov I, Yucus C, Pham A, Garduno L, Szela M, Frigerio R, Maraganore DM: Design and implementation of pragmatic clinical trials using the electronic medical record and an adaptive design. JAMIA Open 2018; 1:99–106
9. Lignou S: Informed consent in cluster randomised trials: New and common ethical challenges. J Med Ethics 2018; 44:114–20
10. Shih MC, Turakhia M, Lai TL: Innovative designs of point-of-care comparative effectiveness trials. Contemp Clin Trials 2015; 45(Pt A):61–8
11. Beecher HK: Ethics and clinical research. N Engl J Med 1966; 274:1354–60
12. Chludzinski A, Irani C, Mascha EJ, Kurz A, Devereaux PJ, Sessler DI: Protocol understanding and anxiety in perioperative clinical trial patients approached for consent on the day of surgery. Mayo Clin Proc 2013; 88:446–54
13. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Vender JS, Landry E: Consent for anesthesia clinical trials on the day of surgery: Patient attitudes and perceptions. Anesthesiology 2016; 124:1246–55