

**Research Universities and Institutions; Medical Centers and Schools of Medicine;
Academic Institutional Review Boards and University and Medical Center Staff –
Preliminary Findings from a Review of Responses to the Common Rule NPRM**

Overview

There were 204 responses in this category. Those responding overwhelmingly commented on proposed changes specific to biospecimens, but many also commented on other areas we queried, including mandated use of a single institutional review board (IRB) for multisite studies, extending the Common Rule to all clinical trials, proposed data security safeguards, and the proposal to post clinical trial consent forms to a federal website.

Biospecimens (94% oppose, 4% support, 2% support with qualifiers)

We reviewed three major proposals specific to biospecimens including the proposal to expand the definition of “human subject” to include non-identified biospecimens, to mandate broad consent for secondary research use of biospecimens and to restrict IRB waiver of consent for secondary research use of biospecimens. Seventy-one percent (145 of 204) of responses included comments on at least one of the three proposed changes. Among those responding, 94% (136 of 145) opposed one or more of the proposed changes, 4% (6 of 145) offered support and 2% (3 of 145) offered qualified support.

Definition of “Human Subject” (94% oppose, 3% support, 3% support with qualifiers)

Fifty-seven percent (117 of 204) of responses included comments on the proposal to expand the definition of “human subject” to include non-identified biospecimens. Among the responses, 94% (110 of 117) opposed the proposed change, 3% (4 of 117) supported it, and 3% (3 of 117) offered qualified support. Those opposed to the proposed change most often cited the potential impact on science and medicine, often associated with impracticability and cost, and suggested that such a change would not increase protections, would reduce the number and diversity of biospecimens and would potentially increase the potential for a de-identified biospecimen to be identified.

“We strongly feel that implementing the proposed changes would have lasting negative effects on basic research, affecting the ability to prevent, treat and cure human disease worldwide and affecting the quality of life for those of us living today and for generations to come.”

“[We are] concerned that upon full implementation of the final Rule, legacy collections of residual clinical samples obtained without documented consent for research use would need to be deidentified, per a proposal in the NPRM, severely limiting their potential value in research. This may have a significant impact on precision medicine, rare disease and other initiatives that rely on analysis of many biospecimens obtained from a broad cross-section of the population or from many sources.”

“[Our university] believes the NPRM's proposed changes will not provide meaningful information to the public, will reduce protections for the public through retention of identifiers as a means to verify consent, will result in a significant reduction in available biospecimens and [have a] negative impact on our understanding of health and disease, will reduce the diversity of biospecimens used in research and would be so costly that many researchers, universities, hospitals and clinics will simply find implementation of the proposed changes unaffordable.”

“We do not think that implementation of a plan that will cost many billions of dollars without significantly enhancing subject protections represents responsible stewardship of precious research resources.”

Limited support for the proposed change typically cited identifiability and ethical principles.

“Advances in technology and respect for the public’s willingness to share biospecimens make it an appropriate step to add additional oversight for research involving biospecimens.”

Alternative Proposals

Of those opposed to changing the definition of “human subject”, 19% (22 of 117) suggested that if a change were made they would prefer Alternative A – expanding the definition of “human subject” to include whole genome sequencing, suggesting that this represented a more balanced approach than the primary proposal. One expressed support for Alternative B if a change were made – classifying certain biospecimens used in particular technologies as meeting the criteria for “human subject,” and one for either A or B. Nine responses explicitly stated that none of the proposed changes were acceptable, as suggested in the following comment, “We do not support either alternative, as they will limit important research without enhancing participant protection.” A number of responses suggested that it was unnecessary to change the definition of “human subject,” because if the type of research performed and/or evolving technology rendered a biospecimen identifiable, it would then be subject to the Common Rule under the current definition.

“Alternative A seems the most reasonable. However, the requirements for consent (and data security) under Alternative A should be based on the intent to create a whole genome data set and the maintenance of that set rather than on use of the biospecimen itself. Furthermore, sharing a subset of that genome data without individual subject identifiers should be considered non-identifiable (and, hence, not meeting the definition of ‘human subject’) and not be subject to any further consideration under the rule.”

“Flexibility allows each IRB to consider regional norms and move forward with definitions and operations based on the current state of technology and risk to research participants. What was readily ascertainable 10 years ago has changed and will be different 10 years from now. This allows IRBs and researchers to assess identifiability based on current technology, data sharing and computing capabilities, as opposed to

comparing it to a prescriptive or inclusive list of identifiers or scientific technologies provided by OHRP as part of the federal regulations.”

Broad Consent (91% oppose, 4.5% support, 4.5% support with qualifiers)

Sixty-three percent (129 of 204) of responses included comments specific to the proposal to require broad consent for future unspecified research use of biospecimens. Of these, 91% (117 of 129) opposed the proposal, approximately 5% (6 of 129) supported it and approximately 5% (6 of 129) offered qualified support. Notice and opt-out were supported in 10% (20 of 204) and 8% (17 of 204) of comment letters respectively. Rationales for opposition to and support for broad consent were similar to that indicated in response to changing the definition of “human subject,” although there was a greater emphasis from those opposed on the combined impact on science and medicine and associated impracticability and cost.

“We are skeptical that the NPRM will enhance protections for research participants and are convinced that the changes will initiate new delays, burdens, and impediments to biomedical discoveries. We question whether such a seismic shift in federal policy to mandate informed consent for biospecimens research is in line with the public’s wants, needs, or interests. We urge you to consider more thoroughly the costs and practical implications of the policy. The burden of regulatory changes to biospecimen research will be considerable, particularly the burdens of operationalizing the consent process and building a reliable tracking infrastructure. Tracking infrastructure will be required regardless of whether the governance relies on an opt-in or opt-out approach. These costs will need to be absorbed by the biomedical establishment or passed onto individuals.”

“Many academic medical centers receive clinical samples that are collected at community hospitals and clinics, surgical centers and private medical practices. Since many of these entities are not pursuing their own research agendas, they would need significant financial and technical resources to incorporate a broad consent process into their existing permission to treat and surgical consent processes, to record and honor that choice, and to transmit that information compatibly with upstream information systems to ensure compliance with the NPRM.”

“This document [the NPRM] represents a real missed opportunity to reduce and streamline regulatory burden. Of note, our data...has shown that 1% of ~20,000 de-identified specimens that are stored for potential future research are used for that purpose. Is the burden to obtain informed consent imposed on patients and investigators warranted? We suggest that a thoughtful, deliberate and rigorous study of both the problem, and an evaluation of potential workable and affordable solutions by an engaged research community (inclusive of research participants, patients, researchers, academic institutions, health care providers, advocacy groups, foundations and the public) should be undertaken.”

A few comments offered support or qualified support for the proposed change:

“In general, we support the proposed definition of human subject to include all

biospecimens regardless of identifiability. Our strong caveat is that access to the wealth of information contained within archival paraffin blocks of tissue (e.g. surgical pathology remnants) procured for clinical purposes before the effective date of the common rule should be facilitated.”

Waiver of Consent (98% oppose, 2% support)

Twenty-seven percent of comments (55 of 204) addressed proposed restrictions to waiver of informed consent for secondary research use of biospecimens by an institutional review board, with 98% (54 of 55) opposed to the restrictions and 2% (1 of 55) in support of the proposed changes.

“We believe that the current guidance, requiring IRB review of individual secondary research projects but permitting the IRB to waive the consent requirement in appropriate circumstances, is actually more protective of subjects than the proposed revision.”

“Rather than seeking to implement a new process that is potentially hugely burdensome and that by its nature is unable to anticipate the extent of future research uses and inform subjects accurately about those uses, the existing waiver of consent process should be retained, and as necessary, improved.”

Single IRB (89% oppose, 8% support, 3% support with qualifiers)

Regarding mandated use of a single IRB for multisite studies, 58% (119 of 204) of responses included comments, of which 89% (106 of 119) opposed the mandate, 8% supported it (10 of 119) and 3% (3 of 119) offered qualified support. Limited support generally came from medical schools and health systems. Among those opposed, many suggested that a single IRB would not decrease cost and administrative work in most instances and was not appropriate for all studies, including, but not limited to, social and behavioral studies, studies with a different focus and protocol at different sites, studies with few sites and studies involving special populations.

“While single-IRB review for multi-site cooperative research is appropriate for some studies (those where activities and procedures are largely uniform across study sites), there are many other examples of cooperative research in which it is not appropriate or realistic.”

“Differences in institutional policies and procedures, scopes of work at each site, and local cultures can make the negotiation and maintenance of a reliance agreement more onerous and time-consuming for investigators and IRBs, and less protective of the interests of research participants. The only scenario for which we see the mandate for use of a central IRB adding value is when a study involves identical procedures and involvement at each site. In these instances, however, it seems more appropriate for the funding agency to require the use of a single IRB, rather than a mandate being codified in the regulations.”

“We believe that requirement of a single IRB is premature at this time as there is a lack of validity of data at the individual institution level. In addition, a lack of required resources to create tools and absorb the costs of operation as well as administrative burden to functionalize this process would cause major roadblocks in effective implementation...”

Extending the Common Rule to All Clinical Trials (78% oppose, 7% support, 21% support with qualifiers)

Fourteen percent (29 of 204) of responses addressed the topic of extending the Common Rule to all clinical trials regardless of funding source at institutions that receive federal funding for non-exempt and non-excluded human subjects research. Of these, 72% (21 of 29) opposed the proposed measure, 7% (2 of 29) supported it and 21% (6 of 29) offered qualified support. Those offering qualified support indicated support for particular types of studies such as those greater than minimal risk.

“...the University does not believe that this proposed extension will materially improve oversight of such studies, but will increase reporting burdens on institutions and researchers. The University does apply equivalent protections to human research subjects in all studies conducted at the University, relying upon the Belmont Report to guide its oversight of such research where there is no federal funding. In our experience, this approach has not resulted in any material diminution in the protections that those research subjects are afforded.”

“As a research intensive university, many of our students and residents engage in research which would meet the proposed definition of a clinical trial and thus would be subject to the Common Rule. Extending the Common Rule to these trainees would create a significant administrative burden for our institution, as well as OHRP, without providing any additional protection to human subjects.”

“While [our university] is not in favor of extending the Common Rule to all clinical trials ... we would be supportive of such an extension to greater than minimal risk clinical trials.”

Security Safeguards (78% oppose, 11% support, 11% support with qualifiers)

Regarding the proposed security safeguards, 14% (28 of 204) responded, of which 78% (22 of 28) opposed the proposal 11% (3 of 28) supported it and 11% (3 of 28) offered qualified support. Lack of support was primarily in response to the concept of security safeguards promulgated by the Secretary of the Department of Health and Human Services as the proposed safeguards were not detailed in the NPRM.

“Much of the data collected in research is currently regulated under a variety of other state and federal laws, including HIPAA and FERPA. Any data security regulations promulgated under the Common Rule will at least be redundant in many cases or at most could add to the regulatory complexity if they conflict with other regulations. IRBs currently assess data security in the context and nature of the research, the information

collected, and the length and method of retention. Where questions arise, IRBs work with appropriate institutional units to ensure data is protected.”

“We support OHRP’s decision to provide privacy standards/safeguards. We would need to review these new standards/safeguards in order to determine if they will meet the goals of the NPRM.”

“[Our] University strongly supports this proposal as the IRB will not have to assess the confidentiality provisions of each study if the investigator can confirm that specified standards are met.”

Posting Consent Forms (98% oppose, 2% support)

Regarding posting clinical trial consent forms to a federal website, 23% (47 of 204) commented. Ninety-eight percent (46 of 47) opposed the proposed change and 2% (1 of 47) supported it. Those opposed suggested that the proposed change would not improve consent forms and would increase burden and cost.

“The NPRM states that the public posting of consent forms ‘is intended to increase transparency, enhance confidence in the research enterprise, increase accountability, and inform the development of future consent forms.’ However, there are no data to support that posting consent forms will achieve these goals. Furthermore, the proposal allows proprietary information to be redacted from consents prior to posting. A redacted consent would not be seen as being transparent to the public—it would look like information is being purposefully hidden. This seems in opposition to the goal of improving transparency. Based on the cost information in Table 26 of the NPRM, the development and maintenance of a website for posting consents will also come at significant cost to the taxpayers (present value costs of \$14.6 million and annualized costs of \$1.71 million). This does not include the significant costs to investigators or the unfunded administrative burden to institutions. This expense does not seem justified given that there are no quantifiable benefits.”

“A more useful goal and approach would be to attempt to generate a collection of best practice exemplars of outstanding consent documents for a variety of types of studies. This might be a complement to, or in lieu of, the promised future guidance.”

Overarching Concerns

Beyond analyzing responses to the particular NPRM elements elaborated above, we also looked at more general assessments of the status of the NPRM. A quarter of responses in this category (50 of 204) suggested that the NPRM did not meet necessary standards or requirements, called for part or all of the NPRM to be rewritten and republished, and/or suggested that aspects of the NPRM for which details were not included (e.g., the decision tool, Secretary’s list of minimal risk research, Secretary’s security safeguards or the Secretary’s draft consent form) should be published as separate advance notices.

“The urgency to approve a final revised Common Rule prior to the end of 2016 is deeply concerning and has resulted in a premature, rushed document that is replete with deficiencies, contradictions, areas of conflict or overlap with other federal requirements, undefined processes, categories or lists and yet to be developed forms and templates. The lack of availability of these items at this late stage in the rule making process makes commentary particularly challenging.”

“Implementing this rule without substantial revisions will not improve the safety and well-being of research participants and will harm the nation’s ability to realize the progress that could come from the Precision Medicine Initiative and other badly needed health research.”

“It is worth noting that the professionals who have committed years of their lives to implementing the current Common Rule regulations during the course of these changes have expressed almost universal dismay at what has been issued. Serious rulemaking cannot be so opaque that those who live and breathe the current regulations and issues cannot fully grasp the NPRM and requests for public comment.”

University Responses by Level of NIH Support

We reviewed responses to three major provisions, expanding the definition of “human subject” to include non-identified biospecimens, obtaining broad consent for biospecimen storage and potential research use, and mandating the use of a single IRB for all multisite studies among institutions receiving the highest levels of NIH support. Of the top 10 institutions ranked by level of NIH support, 100% responded and all oppose these three major provisions of the NPRM.

Taking the top 40 ranked institutions, 80% were opposed to the provisions and only 5% were supportive, with 88% responding. These top 40 institutions receive 76% of NIH funding. This data speaks to very serious concerns about these critical provisions of NPRM among those investigators and institutions that NIH entrusts with most biomedical research on behalf of the nation. Opposition was also expressed to other elements, such as treating many quality improvement/quality assurance activities as human subjects research.