

Advisory and Related Groups – Preliminary Findings from a Review of Responses to the Common Rule NPRM

There were six responses in this category, including: The Presidential Commission for the Study of Bioethical Issues; the Department of Health and Human Services (DHHS) Secretary’s Advisory Committee for Human Research Protections (SACHRP); comments from individual members of the National Academy of Medicine Leadership Consortium for Value and Science Driven Health Care’s Clinical Effectiveness Research Innovation Collaborative (CERIC); the (DHHS) Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC); Public Responsibility in Medicine and Research (PRIM&R); and the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

Advisory and related groups largely focused on major proposed changes, including the treatment of biospecimens and a proposed mandate for use of a single IRB for multisite studies. The groups largely expressed opposition to the proposed changes.

Biospecimens (100% oppose)

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. Eighty-three percent (5 of 6) of responses included comments on at least one of the three proposed changes. Of these, 100% (5 of 5) opposed the proposed changes.

“Because research infrastructure in academia and industry has been premised on this existing regulatory structure and because transition costs for a radically different regulatory structure could be steep, a major shift in federal policy in this area must: (1) significantly enhance the protection of human subjects in research, (2) not impede medical innovation, research, and development, (3) be supported by empirical data and/or compelling policy reasons, and (4) be consistent with the principles identified in the Belmont Report of respect for persons, beneficence, and justice.” – SACHRP

“This process will require significant resources on the part of institutions that collect biospecimens; it will be entirely out of reach for small healthcare institutions and community and school-based clinics, and may very well be beyond the capability of some larger and better-resourced institutions.” – PRIM&R

Definition of “Human Subject” (100% oppose)

Sixty-seven percent (4 of 6) of responses included comments on the proposal to expand the definition of “human subject” to include non-identified biospecimens. Among the responses, 100% (4 of 4) were opposed to the proposed change. Of those opposed to changing the definition, 33% (2 of 6) suggested that if a change were made they would prefer Alternative B – classifying certain biospecimens used in particular technologies as meeting the criteria for “human subject.”

The Presidential Commission for the Study of Bioethical Issues, in its comment letter, has suggested that Alternatives A and B, are “superior to the primary proposal” and more likely to result in increased trust in the research enterprise. The Commission points out that “Alternative B considers all research using “bio-unique” data as human subjects research. This proposal puts the focus on the technology and its ability to identify donors using small amounts of data, as opposed to tying the definition of human subjects research to a particular kind of data, whole genome sequencing data, which we know can identify individuals today.” In addition, the Commission suggested that the primary proposal [requiring broad consent for all non-identified biospecimens] is inconsistent with the ethical rationale described in the NPRM and will stall certain kinds of research using deidentified biospecimens that pose no risk to human subjects and that are unlikely to impact participants’ autonomy interests, stating “Autonomy is implicated when biospecimens can be linked to individuals, but when there is no possibility of identifying the donor, autonomy and respect for persons are less relevant.”

“...when blood samples are taken for clinical purposes, and the leftover blood is sent to a laboratory where an investigator might conduct basic science research, such as comparing the pathology of samples from different kinds of individuals. Because the samples are stripped of identifiers, and the research does not involve bio-unique information such as genomic sequencing, there is no risk of being able to re-identify the donors. The donors are aiding in the scientific endeavor with no risk to themselves. Although they might express an autonomy interest in what happens to their samples, it is very difficult to separate autonomy from identifiability.” - The Presidential Commission for the Study of Bioethical Issues

Broad Consent (100% oppose)

Fifty percent (3 of 6) of responses included comments specific to the proposal to require broad consent for future unspecified research use of biospecimens. Of these, 100% (3 of 3) opposed the proposed change. Thirty-three percent (2 of 6) of those responding proposed notice and opt-out as an alternative to broad consent.

SACHRP has recommended public education, notice to patients about research practices, providing an opportunity to “opt-out” of future research use of their biospecimens and identified data, and “limitations and sanctions on unauthorized re-identification” as an alternative to a broad consent mandate they suggest would “meet none of the basic requirements of the traditional doctrine of informed consent” and could “substantially hamper scientific progress.”

“To the extent that the NPRM’s core proposal is meant to ensure that subjects provide meaningful consent to future research with biospecimens and to prevent biospecimen re-identification, the NPRM would do nothing of the sort.” – SACHRP

“PRIM&R has identified substantial ethical, conceptual, and practical problems with these proposals and recommends that the regulations in this domain not be changed at this time, in order to allow further study of alternatives.” – PRIM&R

“To include all biospecimens, specifically newborn screening RDBS [residual dried blood spots], as human subjects may hinder research and innovation and could ultimately not provide additional protections to individuals. In addition, a broad definition could hinder the development of new newborn screening tests and important public health activities would be jeopardized.” – ACHDNC

Waiver of Consent (100% oppose)

Thirty-three percent (2 of 6) of responses included comments on the proposed restrictions to IRB waiver of consent. Of these, 100% (2 of 2) opposed the proposed restrictions. SACHRP has recommended “that HHS revise the waiver criteria at §.116(f) to allow an IRB to approve the storage, maintenance, and secondary research use of biospecimens collected for non-research purposes without the prior provision of notice of research practices and an opportunity for opt-out” provided certain conditions are met.

Single IRB (75% oppose, 25% support)

Regarding mandated use of a single IRB for multisite studies, 67% (4 of 6) of responses included comments on single IRB. Seventy-five percent (3 of 4) of those responding opposed the proposed change and 25% (1 of 4) supported it.

“A concern to SACHRP is the possibility that requiring a single IRB to review a multi-site research protocol may well result in new procedures and policies being created by the relying...and reviewing IRB...that could undermine the goals of this policy change and create a host of new challenges for research institutions. There is a significant difference between an entity like the NCI CIRB which is in the business of serving as a central reviewing IRB and the rotation of the single IRB function among institutions who will serve this role for some research protocols and not for others. It takes an enormous investment in IT resources and databases to manage the communication flows, state law and local context issues for different institutions as well as the divergent policies and processes of each institution.” – SACHRP

“With a number of concerns and reservations, as described below, AAHRPP supports generally the notion that single IRB review of multi-site studies can be an effective and efficient way to review and approve human research. However, there are so many open questions relating to the NPRM as written that its promulgation as a Final Rule "as is" would be a mistake. While, on its face, this may appear to be a rational approach, it is not clear whether this "one size fits all" requirement will actually lessen institutional burden, given the infrastructure and administrative complexity of becoming or ceding to a single IRB of record. AAHRPP recommends that the choice of using a single IRB be determined on a case-by-case basis, accompanied by guidance that provides assistance in creating and using cooperative agreements to address the complex nature of relying on a single IRB for review. AAHRPP does not believe the current proposal for mandated single-IRB review is ready to be issued as a Final Rule.” – AAHRPP

“This change will remove inefficiencies from the oversight process without compromising protections for human participants.” - Individual members of the National Academy of Medicine Leadership Consortium for Value and Science Driven Health Care's Clinical Effectiveness Research Innovation Collaborative – CERIC

Posting Consent Forms (67% oppose, 33% support with qualifiers)

Regarding posting clinical trial consent forms to a federal website, 50% of responses included comments. Of these, 67% (2 of 3) opposed the proposed change and 33% (1 of 3) supported it with qualifiers.

“AAHRPP believes that the requirement in the NPRM for the posting of informed consent documents on a public website is ill-advised as a matter of policy. Such a requirement will add significant burden to institutions and investigators with no corresponding benefit to human participants; and, as free-standing documents divorced from context, posting these materials could have the unintended and diametrically adverse consequence of reinforcing the concept of the supremacy of the form over process in informed consent.” – AAHRPP

“In general, SACHRP endorses a requirement for posting consent forms, but recommends strongly that OHRP develop robust guidance to minimize confusion about implementation of the rule, reduce the risk that posted consent forms will be misunderstood or misused, and maximize the ability of investigators, institutions, and regulators to review posted consent forms in order to learn and improve the consent form and process.” – SACHRP

Additional Areas of Concern

Advisory and related groups did not respond to a proposed change to extend the Common Rule to all clinical trials. One response on proposed data security safeguards expressed opposition to the proposed change.

“SACHRP believes that the protections currently proposed in §_.105 would be too extensive, burdensome, and rigorous for the minimal risk posed by the storage, maintenance, and secondary research use of de-identified biospecimens. Thus, SACHRP recommends that HHS develop a new, broad scheme that would require institutions, researchers, and authorized recipients of de-identified biospecimens only to establish appropriate and calibrated protections to prevent, or minimize the risk of, the unauthorized release, access, or use of de-identified biospecimens.” – SACHRP

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. Fifty percent of responses in this category (3 of 6) suggested that the NPRM did not meet necessary standards or requirements and called for part or all of the NPRM to be rewritten and republished.

“SACHRP recommends that HHS conduct a comprehensive re-write of the NPRM through a concerted effort to simplify the proposed changes and to focus efforts on selected issues for which there is broad support by the public, investigators, IRB professionals, sponsors and other experts. Prior to the publication of final rules, SACHRP supports a second publication of a NPRM that presents a simplified, focused set of proposals for further public consideration and comment.” – SACHRP

“...it is AAHRPP's view that, taken as a whole, there remain many significant issue areas within the proposal that need to be addressed more coherently and comprehensively before they are reasonably amenable to promulgation as final rules, or, perhaps dropped altogether as areas of new or newly complicated regulation.” – AAHRPP

“We recommend that the relevant agencies pursue an issue-by-issue approach in which it is possible to “drill down” on an issue, to consider all the sections of the regulations where it arises and all the evidence that is available—and that is needed—to resolve it well. Further, the agencies should address each issue more openly, developing and relying upon evidence, and allowing consensus to emerge and revisions to be crafted that will work well for all stakeholders. This approach would not only produce better results, but would signal that, once adopted, any provision can be changed if it does not work as well as intended.” – PRIM&R