Analysis of Public Comments on the Common Rule NPRM

The following preliminary comments derive from an effort led by the Council on Governmental Relations (COGR), with support from the Association of Public and Land-grant Universities (APLU), to review and analyze the 2,186 public comments submitted in response to the 2015 "Federal Policy for the Protection of Human Subjects" or "Common Rule" Notice of Proposed Rulemaking (NPRM) (Table 1). Analysis methods are outlined in Appendix A.

The associations reviewed a number of major proposals in the NPRM, 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 Institutional Review Board (IRB) waiver of consent for secondary research use of biospecimens. Also reviewed were proposals to mandate use of a single IRB for multisite studies; extend the Common Rule to all clinical trials regardless of funding source at institutions that receive federal funding for human subjects research; proposed standard security safeguards; and, the proposal to post clinical trial consent forms to a federal website. In addition, general assessments of the status of the NPRM were considered.

The results of our review (Table 2) find significant opposition to most major proposals, with mixed support for mandated use of a single IRB and extending the Common Rule and greater support for the concept of standard security safeguards. In addition, a number of responses suggested that the NPRM is overly complex, poorly written, and not supported by data; highlighted areas that could have a substantial impact on a final rule but were not included in the NPRM (e.g., proposed security safeguards, a consent template, a list of minimal risk studies and a decision tool); and suggested that some of the proposals would adversely affect human health with little perceived benefit.

Non-identified Biospecimens

Among the major proposals to update the Common Rule are provisions that would expand the definition of "human subject" to include non-identified biospecimens. The premise for this change is respect for autonomy, one of the three core principles of the Belmont Report which are central to the Common Rule requirements. The proposed change would require broad consent for future unspecified research use of biospecimens in all but a limited number of circumstances, including biospecimens obtained in non-research settings in the course of clinical care. Under the current Common Rule these specimens, and those obtained through research, can be stored and used in secondary research by obtaining an IRB waiver of consent. Under the proposed rule, waiver of consent for secondary research use of biospecimens would be "rare." The NPRM

suggests that this will increase trust and that "an increase in trust and partnership is likely to increase participation rates in research."[1]

Patients and the Research Community Overwhelmingly Oppose the Proposed Changes

The majority of responses, approximately 1,520, addressed one or more of the proposed changes detailed above involving non-identified biospecimens. Of these responses, 94 – 100% of patients and members of the research community, including researchers, universities, medical centers and industry, opposed the changes. Those commenting suggested that the proposed changes will significantly reduce the availability of biospecimens for research, will have a significant negative impact on medical advances, and will adversely affect human health. Per one patient, "I am asking for life saving policy not life ending policies." From a biorepository, "Respecting autonomy at the expense of patient lives is a significant ethical concern."

Advisory and related groups were similarly opposed. The Presidential Commission for the Study of Bioethical Issues, in its comment letter, suggested that the primary proposal to expand the definition of "human subject" to include 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 are unlikely to impact participants' autonomy interests. The Department of Health and Human Services (DHHS) Secretary's Advisory Committee for Human Research Protections (SACHRP) concluded that "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."

Opposition to the proposed changes related to biospecimens ranged from 67% to 79% among health departments, disease registries, professional associations, biorepositories and independent IRBs. Cancer registries commenting on the proposed changes to the treatment of biospecimens opposed them, suggesting they would severely limit scientific breakthroughs and not grant additional autonomy. The rationale for the latter presumably being that the majority of biospecimens collected during clinical care will never be used in research; that research use cannot be predicted at the time of collection and therefore only generic information about potential use could be provided; and that many research uses would not result in bio-unique information, and therefore risk of identification.

---

[1] Federal Policy for the Protection of Human Subjects. Pg. 53944 Retrieved from: https://www.federalregister.gov/articles/2015/09/08/2015-21756/federal-policy-for-the-protection-of-human-subjects

> "With precision medicine now a mandated national priority, there is tremendous focus on the development of targeted therapies which requires the identification of representative sets of biospecimens for research. While research could, in theory, be performed utilizing biospecimens for which consent was obtained, the inherent limitations of such a restriction could negatively bias efforts in cancer research in this field."

Members of the Public Not Identifying as Patients are Divided

Among members of the general public, 55% opposed and 45% supported one or more of the major proposed changes related to biospecimens. Support was largely provided in response to a December 30, 2015, New York Times opinion piece by Rebecca Skloot, author of the book *The Immortal Life of Henrietta Lacks*, which provided a link to the proposed regulations and encouraged readers to respond. The views in that op-ed were countered in other publications including an opinion piece by Michelle Meyers, Assistant Professor and Director of Bioethics Policy in the Clarkson University-Icahn School of Medicine, in Forbes which suggested that the op-ed may serve to "miseducate" the public, and the Wall Street Journal opinion piece How Not to End Cancer in Our Lifetimes, by Laurie Glimcher, Dean of Weill Cornell Medicine and Provost for Medical Affairs of Cornell University.

Responses from advocacy groups were also mixed, with 23 comments in support of the proposed changes and 21 opposed. However, when grouped by general citizen and privacy advocacy; cancer and rare diseases; and other disease and disorder advocacy groups; we found that the former group focused more on information and privacy issues and were more likely to support the proposed changes while groups representing those with rare diseases and forms of cancer, those most likely to be negatively impacted by the proposed changes, were most likely to strongly oppose them (Table 3).

Those opposed to the changes often cited the substantial negative impact on research and human health, and perceived few if any benefits. Many expressed concern about the significant loss of available biospecimens going forward, due to the proposal to obtain broad consent and the potential loss of archived specimens due to proposed restrictions to the current waiver criteria. Per one response, "This would set back human subjects research substantially and delay or prevent the acquisition of life-saving knowledge." And another, "The harm of denying patients cancer therapy [is] more probable than the potential harms associated with unconsented use of these tissues."

Those in favor of the proposed changes tended to cite moral and ethical principles, while some indicated concern about identifiability. These respondents were not aware of concerns expressed about necessary infrastructure, and the potential cost and impact, of mandating broad consent. Per one response: "I suspect there is a wish that the public remain ignorant about this for fear that

we will demand protections that would inconvenience researchers who would rather not be bothered, and that makes me even angrier." And another, "I strongly agree with these proposed changes. I feel that the old laws were put in place before modern technologies made reverse identifying of 'anonymous' specimens possible. I also believe that many if not most subjects will be willing to allow their cells to be used and that it will be fairly straight forward to administer consent forms to subjects. Therefore, it should not hinder research."

Definition of "Human Subject" and Alternative Proposals

There were 1,083 responses addressing the proposal to expand the definition of "human subject" to include non-identified biospecimens. This review finds that 86% of biorepositories; 90% of patients; 94% of researchers, universities and medical centers; and 100% of industry groups, disease registries and advisory groups oppose the proposal. Approximately 67% of professional associations and health departments opposed the proposed change while responses from advocacy groups and the general public were mixed, with 61% of the general public and 46% of advocacy groups opposed to the proposed change and 39% and 54% in support, respectively.

Per one patient: "Please don't put the remote chance of invading the privacy of some patients ahead of the lives of others." And another: "We need this continued research. I would challenge any person who discovers this disease exists within themselves or a loved one to deny the continued research with any and all tumor tissue available. There is no good reason to deny access to all discarded tissue."

From a researcher: "We are at a time in history when we have the technology to begin to answer some of the fundamental questions regarding human disease, and when we can start to truly trial targeted disease-specific therapies. Please make it easier, not harder, for physician scientists such as myself to understand, diagnose and treat disease."

Approximately 40% (320 of 798) of those opposed to the primary proposal to change the definition of "human subject" to include all non-identified biospecimens indicated that if a change were made, they would prefer Alternative A – expanding the definition of "human subject" to include whole genome sequencing, rather than including all biospecimens. Twelve responses indicated a preference for Alternative B if a change were made – classifying certain biospecimens used in particular technologies as meeting the criteria for "human subject," and one preferred a combination of Alternatives A and B. These findings should not be viewed as an endorsement of the alternative proposals. Almost without exception, those recommending the alternative proposals opposed the primary proposal to expand the definition of "human subject" and suggested that if OHRP were to move forward with one of the proposals despite strong opposition, Alternative A (or in some instances B) would have the least negative impact on

research and human health. This more limited change would apply the regulations to research that has the potential to result in the identification of the donor, without impeding broader research efforts that pose little or no risk of identification. The Presidential Commission for the Study of Bioethical Issues indicated support for modifying the Common Rule in accordance with Alternative Proposal B, suggesting that this proposal considers all research using "bio-unique" data as human subjects research.

Broad Consent

Fifty-three percent of responses (1,055) included comments on broad consent. Of these, 62% (652 of 1,055) opposed the proposed change, 22% (237 of 1,055) supported it and 16% (166 of 1,055) offered qualified support. Eighty-five to 100% of patients; universities, medical centers and affiliated IRBs; advisory and related groups; and disease registries opposed the proposal to mandate broad consent for the storage and secondary research use of biospecimens.

Per a patient: "If you don't have a rare disease then you don't understand the ramifications of no studies because of no samples because of a consent form. Please it's diseased dead tissue, nobody wants to keep, we as patients need research and testing done."

SACHRP has recommended public education, notice to patients about research practices, providing an opportunity to "opt-out" of the future research uses 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." Among those commenting on broad consent, 114 (approximately 6% of responses) suggested notice as an alternative to broad consent and 138 (approximately 7% of responses) opt-out rather than opt-in. The National Academy of Sciences Committee on Federal Research Regulations and Reporting Requirements, in its 2015 report, stated that "requiring consent for all research involving biospecimens, as contemplated by the Advanced Notice of Proposed Rulemaking (ANPRM)[2], would substantially increase administrative burdens on investigators, research staff, and institutions, and would markedly hinder the conduct of critical science."[3]

From a research university/medical center:

---

[2] An ANPRM for revision to the "Common Rule" regulations for human subjects' protections was published by the Department of Health and Human Services (HHS) in July of 2011.

[3]Retrieved from: http://www.nap.edu/catalog/21803/optimizing-the-nations-investment-in-academic-research-a-new-regulatory

> "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."

Sixty-seven percent of researchers and independent IRBs opposed the proposed change. Specifically, among researchers 6% (12 of 196) supported it and 27% (53 of 196) offered qualified support. Pathologists offered qualified support using a form letter provided by the American Society for Investigative Pathology (ASIP). Per the letter, "If non-identified biospecimens are redefined as human subjects, we urge consideration of opt-out broad consent models for non-identified biospecimens collected in both research and non-research settings." Opposition from biorepositories, professional associations and health departments ranged from 55% to 64%.

Support for broad consent was mixed among the general public with 32% (183 of 562) of the public in support of the proposed change, 15% (83 of 562) offering qualified support and 53% opposed. Fifty-seven percent of advocacy groups and 53% of industry groups supported the proposed change. Those in favor of the proposed change tended to cite ethical principles while some indicated concern about identifiability. Among those in favor of requiring consent, 23% wanted specific, rather than broad, consent. Per one member of the public: "Please allow ME to decide if I wish to have my tissues made available for research or not. It is the polite and moral thing to do." And another: "As a private citizen and layperson I feel that it is my right to know how the cellular material collected from me and from my young children will be used. The world is awakening to the necessity for regulation of the use of personal information in all regards and it would be wise for the United States to be current in its policies in order to protect its citizens."

Members of the public opposed to the proposed change cited the substantial negative impact on research and human health and the prohibitive logistics and cost. They suggested that broad consent would not provide meaningful information. Per one response: "The harm of denying patients cancer therapy [is] more probable than the potential harms associated with unconsented use of these tissues." And another:

> "The scope of infrastructure that will need to be created and maintained to effectively capture and track consent to a degree that medical research can carry on unhindered will be enormous. Would the government plan to offer any financial or logistical support towards this endeavor? The burden of tracking consent will be too large for many hospitals to bear alone; this would have a grave negative impact on areas of research."

Tribal governments responding to the NPRM opposed the proposal to make biospecimens collected with broad consent exempt from IRB review. Under the current regulations, an IRB would review applications for secondary research use of biospecimens and the proposed data security measures and grant a waiver of consent as appropriate. SACHRP, in its comment letter, suggested that IRBs should consider data or biospecimens that are identifiable to a particular individual or group as requiring higher standards for protection.

Waiver of Consent

Twenty-eight percent of responses (555) included comments on proposed restrictions to IRB waiver of consent. This area particularly concerned patients. Ninety-one percent of responses from individuals who identified as patients commented on proposed restrictions to use of waiver. Consistent with the public comments on the 2011 ANPRM, there is considerable opposition to the proposed changes. Eighty-eight percent of those commenting (491 of 555) opposed the proposed change, and 12% (64 of 555) supported it. One hundred percent of patients, researchers, industry groups and independent IRBs and 98% of universities and medical centers, opposed this provision which would make IRB waiver of consent for secondary research use of biospecimens "rare." Seventy-five percent of disease registries; 80% of biorepositories and advocacy groups and 85% of professional associations opposed the proposed change. Responses were mixed among the general public and health departments with 58% and 50% opposed respectively. All comments submitted by tribal nations supported the proposed change.

Per one patient:

> "As a healthcare provider and a person with a rare disease, I strongly believe that the waiver of informed consent by IRBs should continue to be permitted for archival tissues using the waiver criteria in the current Common Rule. Without this waiver, research for many diseases would be difficult, and may become impossible for rare diseases. I do not believe that this current waiver puts patients at risk."

From a researcher:

> "The logic of why only rare approvals should be made is not clear and the NPRM does not address this in the proposal. The NPRM suggests that these changes are in keeping

> with wishes of the American public. On the contrary, I would respectfully submit that the public would be upset if they know that this policy if enforced will eliminate key research that will benefit them and their families, by use of residual samples that would normally be discarded. This issues needs to be viewed under the right context-- in the setting where obtaining informed consent is not practicable-- we believe that patients would be willing to consent to use of residual sample when consent is impractical."

ASIP has suggested that the proposed standards for waiver of consent for the use of biospecimens would be almost impossible to achieve; that no evidence is presented that the current approach has compromised safety; and that the current standards be maintained. Considering the proposed restrictions to waiver, SACHRP noted that:

> "The NPRM would apply transition provisions to biospecimens collected before the final rule's compliance date, if the research use of the biospecimens occurs after 'removal of any individually identifiable information associated with the biospecimens.' Thus, banked biospecimens without relevant consent would only be grandfathered if researchers (i) remove all individually identifiable information, which would exclude coded biospecimens from the transition provisions, or (ii) re-identify, relocate, recontact, and reconsent the human sources of the biospecimens. Otherwise, as currently drafted in the NPRM, such biospecimens would no longer be available for clinical research, especially considering that the NPRM would narrowly confine waiver for biospecimen research, permitting that waiver be granted only in 'extremely rare' circumstances."

SACHRP further expressed the concern that "effectively rendering unavailable such extensive and important troves of medical research would impede scientific research and innovation, and that any efforts to reestablish such biospecimen collections would require extraordinary expenses and resources."

Finally, the National Academies Committee on Federal Research Regulations and Reporting Requirements has recommended "that Congress instruct HHS to work with other agencies to ensure that research involving biospecimens is eligible for a waiver or modification of informed consent, so long as the proposed research meets the conditions for waiver or modification of informed consent as specified in the Common Rule," and suggested that "informed consent should not be required for the use of biospecimens that have been previously collected and are no longer needed for clinical use."

Estimated Regulatory Cost and Impact

In addition to the potential impact on the understanding and treatment of disease, the prohibitive cost and logistics of implementing certain aspects of the proposed rule, in particular proposed changes related to biospecimens, concerned members of the research community, and even some members of the public with knowledge of research and the NPRM proposals. The NPRM estimates that the new requirement to obtain broad consent will cost $12.245 billion over a ten-year period, or more than $1.2 billion annually (approximately 4% of the 2016 National Institutes of Health budget). This does not include the significant costs of documenting and tracking permissible uses of biospecimens. ASIP suggests that the NPRM has underestimated the true financial impact "by a factor of at least ten."[4]

> "The wealth of personnel and IT resources that would be needed to comply with the proposed regulations would be prohibitive in virtually all academic medical institutions in today's economic climate."

> "Broad consent for future use will require extensive tracking and cross-checking, which will result in: significant direct financial costs; an increased need for human resources; an increasing demand on IT infrastructure; and, a resultant decrease in biospecimens available. Small facilities such as clinics will not be able to follow these regulations because of direct costs, requirements for increased staff time and a lack of mission-related benefit… Given that [these] same small facilities are primary providers for underserved, underrepresented and minority populations, this will potentially increase health disparities. Public health in general will suffer."

Mandated use of a Single IRB

The Research Community is Divided on a Mandate for Single IRB

Fifteen percent of responses (308) included comments on the proposal to mandate use of a single IRB for multisite studies. Of these, 51% opposed the proposed change (158 of 308), 42% supported it and approximately 6% offered qualified support. A handful of researchers independently expressed support. However, support from researchers was expressed primarily through form letters developed by ASIP stating: "I support mandatory single IRB review of all cooperative research and recommend that the single IRB of record also be charged with approving the protocol and the consent." Seventy-five to 83% of advocacy groups, professional societies, disease registries and independent (commercial) IRBs supported the proposed change. Eighty-nine percent of universities and medical centers opposed the

[4] Retrieved from: http://www.asip.org/SciencePolicy/documents/ASIPCommentsNPRMCommonRule.pdf

provision. Limited support was generally drawn from medical schools and centers. Tribal governments also opposed a mandate for single IRB:

> "By promoting the use of a single IRB in cooperative and multi-site research, these proposed revisions do not foster community-based governance and oversight of research that has the potential to improve outcomes for tribal and minority populations."

Most data registries supported the proposed mandate:

> "NCCR has long supported the proposed requirement that a single Institutional Review Board (IRB) be utilized for most multi-site research studies. A central IRB model will improve the efficiency of clinical trials, increase collaboration among trial sites and investigators, reduce or negate the need for multiple IRB reviews at the local institution level, provide consistency across clinical trial sites, help achieve potential cost savings and ultimately accelerate the translation of biomedical discoveries to new cancer therapeutics."

However, one expressed concern about the additional infrastructure needed to implement the policy:

> "Consistent with the mainstream view of the research community in general, we support migrating to a single IRB for domestic multi-site studies. Meaningful models currently exist, including the National Cancer Institute (NCI) central IRB. The concept put forward through the NPRM though is ill-defined and has the potential to create a myriad of problems. As proposed, what is being discussed is a constantly varying and unpredictable patchwork of rotating IRBs (often on a sporadic or one-time only basis). There is real potential for IRB shopping under this framework that could proliferate a race-to-the-bottom for less rigorous review. Such an approach neither streamlines the IRB process nor improves patient protections."

Those supporting the changes suggested that the proposed change would streamline operations and reduce delays in research. Those opposed to both the Common Rule proposal and the NIH Single IRB Policy that may be released this month (May 2016) suggested that a single IRB, as structured and proposed in the Common Rule and NIH policy, would not reduce delays or decrease cost and administrative work in many 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. Several comments also suggested that current federal central IRBs such as NCI's independent IRB should be expanded or that new federal central IRBs

should be created.

Advisory and related groups, including SACHRP and Public Responsibility in Medicine and Research (PRIM&R), largely opposed the Single IRB proposal. Per the Association for the Accreditation of Human Research Protection Programs:

> "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."

SACHRP has expressed the concern 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 institutions… and reviewing IRB… that could undermine the goals of this policy change and create a host of new challenges for research institutions" and noted in its comments on the Common Rule NPRM that:

> "there is a significant difference between an entity like the NCI CIRB[5] 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."

Extending the Common Rule to All Clinical Trials

Four percent of responses included comments on 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, 52% (39 of 75) oppose the proposed change, 37% (28 of 75) support it and 11% (8 of 75) offered qualified support. Universities and medical centers, professional associations and advocacy groups provided the majority of comments. Seventy-two percent of universities and medical centers opposed the proposed measure, 7% supported it and 21% offered qualified support. Among professional associations and advocacy

[5] National Cancer Institute Central IRB (NCI CIRB), https://ncicirb.org/cirb/default.action

groups, 62% and 75% of comments respectively, supported the proposed change. Universities that opposed the proposed measure noted that domestic academic medical centers and institutions of higher education already review all human subjects research through an IRB whether or not this research is regulated by HHS or the Food and Drug Administration (FDA). They further noted that under the current rule they can apply flexibility to reduce administrative burden while maintaining equal protection of human subjects. Universities also suggested that the proposed regulation will increase administrative burden for minimal risk behavioral and social science research that involve randomization without adding protections to the human subjects involved in these trials. They elaborate that the changes will not impact the organizations that likely cause the greatest concern for the public including private hospitals, clinics, or other health-related entities that conduct clinical trials and do not receive federal funds.

Security Safeguards

Six percent of responses (116) included comments on the proposed Secretary's security safeguards. Of these, 33% opposed the proposed change and 67% supported it. Support from researchers (48 responses) was again expressed primarily through an ASIP form letter: "I endorse the following proposals: Proposal to develop standards deemed sufficient to safeguard privacy in addition to those set forth in HIPAA."

Posting clinical trial consent forms to a public website

Approximately 4% (86) of responses included comments on the proposal to post clinical trial consent forms to a public website. Eighty-four percent of responses opposed the proposed change, 12% (10 of 86) supported it and approximately 5% (4 of 86) offered qualified support. Those opposed suggested that the proposed change would not improve consent forms and would increase burden and cost.

> "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."

Overarching Concerns

In addition to reviewing some of the major proposed changes to the Common Rule, we also looked at more general assessments of the status of the NPRM. Five percent of all comments suggested that the NPRM did not meet necessary standards or requirements, and called for part

or all of the NPRM to be withdrawn, rewritten and republished for comment. This included a quarter of responding universities and 15% of professional associations and advocacy groups.

SACHRP has recommended 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."

Per PRIM&R:

> "The NPRM includes proposals that reflect inadequate consideration of important ethical, practical, and logistical implications, for example those related to the requirement for 'broad consent.' Key proposals, such as the mandate for single IRB review, rest on a scant evidence-base and apply untested theories... [T]he NPRM too often offers new regulatory mandates when more flexible and less permanent solutions outside a regulatory framework would be sensible alternatives."

These comments were largely echoed by universities and medical centers:

> The NPRM "Does not meet the standards of a proposed rule. 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."

Public Citizen, a consumer advocacy group, similarly noted that:

> "Multiple provisions of the NPRM make reference to decision tools (e.g., an exemption determination tool), guidance documents (e.g., planned guidance from the Secretary on writing consent forms in language understandable to the subject), model agreements, or document templates (e.g., the Secretary's template document for broad consent to the storage or maintenance for secondary research use of biospecimens and identifiable private information) that have yet to be drafted, which prevents public commenters from fully comprehending the full implications of key parts of the proposed rule. The proposed rule poses 88 detailed and, in some cases, lengthy questions. The responses to those questions and the evaluation of those responses by the departments and agencies that issued the NPRM could substantially alter key provisions of the proposed rule."

Appendix A: Methods

2,186 comments were submitted to Regulations.gov. We categorized comments by "Respondent Type," as indicated in Table 1, using the following categories: Members of the General Public; Patients and Patient Representatives (e.g., Caregivers); Academic Researchers and Medical Practitioners/Researchers; Research Universities/Institutes, Medical Centers, Affiliated IRBs and Employees; Industry/Pharma/Trade Groups; Tribal Governments; Advisory and Related Groups; Independent IRBs or Individuals Affiliated; Health Departments, Officials, Municipal Governments and Epidemiologists; Biorepositories, Affiliated Organizations and Consultants; Disease Registries; Professional Associations and Societies; and, Advocacy Groups.

The following 186 responses were not coded: Responses that were not related to the Common Rule NPRM (25); Materials submitted by OHRP (12); Comments that were withdrawn (8); Responses from individuals who believe they are victims of government-sponsored nonconsensual experimentation and are concerned about exemptions for military and intelligence agency surveillance activities (often utilizing the same or similar form letter) (80); Duplicate submissions (9); Requests for an extension to the comment period (52).

Comments were coded by five university or affiliated organization employees with extensive knowledge of the Common Rule NPRM and human subjects protections using the key below. Codes and comments for each individual response to the NPRM were entered into Excel spreadsheets according to the designated "Respondent Type." Coding was reviewed for consistency and accuracy and any discrepancies resolved with those coding the entries.

Key

1 = Support the proposed change

2 = Support the proposed change with qualifiers (briefly note qualifiers in comments)

3 = Oppose the proposed change

4 = Yes

5 = No

6 = No comment specific to this topic area

Topic Areas/Questions

Biospecimens

1. Does the commenter support or oppose the proposal to expand the definition of human subject to cover research with non-identified biospecimens (obtaining, use, study, or analysis of biospecimens regardless of identifiability)? (NPRM Q1 may have relevant information for all areas/questions; Q2 and 3 biospecimens)

1, 2, 3 or 6

Rationale:

Support: 1 = Identifiability 2 = Ethical principles 3 = Both 4 = Other (note)

Oppose: 1 = Logistics/Cost 2 = Impact on Science 3 = Both 4 = Other (note)

2. Does the commenter indicate which of the three proposals regarding the definition of human subject (including Alternative Proposals A and B) achieves the most reasonable tradeoff between the principles of autonomy versus beneficence? (NPRM Q4 and 5)

A = Alternative A

B = Alternative B

C = Main proposal

<u>Broad Consent</u>

3. Does the commenter support or oppose the proposed requirement to obtain broad (informed) consent for future unspecified research use of all biospecimens regardless of identifiability?

1, 2, 3 or 6

Rationale:

Support: 1 = Identifiability 2 = Ethical principles 3 = Both 4 = Other (note)

Oppose: 1 = Logistics/Cost 2 = Impact on Science 3 = Both 4 = Other (note)

*Note in the comments section if they support or oppose the proposed 10 year limitation on consent for biospecimen collection.

4. Does the commenter recommend public education and/or notice of potential secondary research use of biospecimens collected for research or clinical purposes? (Specify which)

4, 5 or 6

5. Does the commenter recommend that the public have the option to opt-out of potential secondary research use of biospecimens collected for research or clinical purposes?

4, 5 or 6

Consent Waiver

6. Does the commenter support or oppose proposed changes that would limit an IRB's ability to waive consent for secondary research use of biospecimens (and/or identifiable data)? (NPRM Q66-68 may be relevant)

1, 2, 3 or 6

Rationale:

Support: 1 = Identifiability 2 = Ethical principles 3 = Both 4 = Other (note)

Oppose: 1 = Logistics/Cost 2 = Impact on Science 3 = Both 4 = Other (note)

Cooperative Research

7. Does the commenter support or oppose the proposed mandate that all U.S. institutions engaged in cooperative research rely on a single IRB as their reviewing IRB (do they believe it is a realistic option at this time)? (NPRM Q74)

1, 2, 3 or 6

Proposal to Extend the Common Rule to All Clinical Trials

8. Does the commenter support or oppose the proposal to extend the Common Rule to all clinical trials conducted at an institution in the United States that receives federal support for non-exempt human subjects research regardless of the funding source of the specific clinical trial? (NPRM Q85)

1, 2, 3 or 6

Protecting Information and Biospecimens

9. Does the commenter support or oppose the security safeguards and standards proposed for biospecimens and identifiable private information? (NPRM Q71 may be relevant)

1, 2, 3 or 6

*Note rationale in comments where feasible.

Posting Informed Consent Forms

10. Does the commenter support or oppose the proposed provision that would require a copy of the final version of the consent form for each clinical trial conducted or supported by a Common

Rule department or agency be posted on a publicly available federal website that will be established as a repository for such consent forms?

1, 2, 3 or 6

*Please also note in column T if the commenter recommended that the NPRM be revised and republished (or related comments).