American College of Physicians
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(submitted electronically at www.regulations.gov)

Jerry Menikoff, MD, JD
Director
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Docket HHS-OPHS-2015-0008
Notice of Proposed Rule Making, "Federal Policy for the Protection of Human Subjects"

Dear Dr. Menikoff,

The American College of Physicians (ACP) appreciates the opportunity to offer comments on the notice of proposed rulemaking (NPRM) on human subjects research protections, better known as the Common Rule. The American College of Physicians is the largest medical specialty organization and the second-largest physician group in the United States. ACP members include 143,000 internal medicine physicians (internists), related subspecialists, and medical students. Internal medicine physicians are specialists who apply scientific knowledge and clinical expertise to the diagnosis, treatment, and compassionate care of adults across the spectrum from health to complex illness. Many internists contribute to medical research.

General Comments:
ACP shares the goals of the NPRM to modernize and make more effective the regulations for the protection of human subjects. Despite the goal of the NPRM to enhance the protections of human subjects, however, and in answer to Question 1 for public comment, the proposed changes to the regulations do not consistently prioritize enhancing protections for subjects over reducing burdens for investigators. They also do not help to build trust and confidence in how research is conducted. Question 1 gets the priorities backwards when it says: "Public comment is sought on whether the proposed changes will achieve the objectives of (i) decreasing administrative burden, delay and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects."

We agree with the characterization of many of the problems regarding the current Common Rule: that the system does not adequately calibrate the review process to research risk; there are inefficiencies in review of multi-site studies by multiple institutional review boards (IRBs); and there are concerns about the informed consent process; risks associated with use of genetic information, biospecimens and other data; monitoring and evaluation of the current system; adequate protection of all research subjects; and multiple regulatory requirements and variability across IRBs regarding interpretation and implementation. While we largely agree with the diagnosis, the suggested "cures" do not always seem to put subjects first.

We note that the Secretary's Advisory Committee on Human Research Protections (SACHRP) has called for a comprehensive rewrite of the NPRM to simplify and focus the proposed changes. SACHRP commented that, "Despite extensive study of the NPRM in collaboration with numerous colleagues, the universal assessment is that the proposals are virtually impenetrable due to opaque language, unclear concepts, the overlapping nature of various elements, and the intricate relationships of elements to one another. A common refrain is, "If we cannot understand this, where will that leave the average IRB, administrator, and investigator?"" We agree.

ACP also agrees with SACHRP, Public Responsibility in Medicine and Research (PRIM&R) and others who have recommended formal and comprehensive research ethics education programs along with clear delineation of investigator responsibilities, a lost opportunity not addressed in the NPRM.

Further, the NPRM discussion of ethical principles in research and its treatment of "beneficence" emphasize beneficence for society, which leads to conclusions that are not appropriately protective of human subjects (see ACP's specific comments below). The Belmont Report notes the concept of societal beneficence but its main focus is beneficence toward the individual. It says, "In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms. The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others." According to the Belmont Report, this would be true even were the individual to give consent. Beneficence, first and foremost, is about beneficence toward the individual--not the individual's virtue of benevolence in volunteering for research, which the NPRM equates with beneficence. Proposed research must do no harm to the subject/patient, determine if she/he can be benefited and *then* weigh the good to society in doing the research.

As the Belmont Report states, "Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence." The NPRM takes an inappropriately narrow view of what constitutes harm and fails to account for the appropriate application of the principle of beneficence, subject welfare and subject dignity interests.

Additionally, the NPRM frequently speaks of the principle of autonomy when the principle at stake is actually respect for persons, which is broader and includes respect for autonomy.

The NPRM's fundamental misinterpretation of the Belmont Report and research ethics principles has resulted in proposals that are not sufficiently protective of human subjects.

Comments on Specific Proposals:

Excluded and Exempt Research Categories

The list of activities proposed for exclusion from the Common Rule under the NPRM is much too broad. ACP disagrees with including the proposed activities listed under "excluded" that are, in fact, research. The excluded category makes sense for activities that are not research such as quality improvement for the implementation of accepted practices and public health surveillance. Activities now under "excluded" that are "research" should be included under exempt research. In addition, there needs to be accountability for exclusion determinations. They should be documented and periodic audits should be required be done by the institution to ensure determinations are being made correctly.

We are pleased to see our recommendation in response to the 2011 ANPRM for development of a decision tool for more standardized review now proposed in the NPRM. However, exemption determinations using the decision tool should require documentation and regular audit by the institution. A tool should also be developed for exclusion determinations.

In both of these areas—excluded and exempt categories-- the proposed rule does not give sufficient weight to the importance of informational risks and puts too much reliance on determinations that would be made by investigators alone, eliminating necessary checks and balances. It is also extremely difficult to assess a tool that does not yet exist, so these recommendations are dependent on the development of a useful and appropriate tool.

Further, it does not appear that the NPRM gives consideration to the fact that journals require meaningful human subjects review for publication, more necessary checks and balance on the research enterprise.

Continuing Review

ACP agrees with the proposal to eliminate the continuing review requirement for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing data or involve only observational follow-up in conjunction with standard clinical care. We would, however, require continuing review if a study involved cognitively impaired subjects.

We also support the publication and regular update of a list of activities considered to pose minimal risk, a helpful proposal.

Biospecimens and Identifiable Information

ACP agrees with the change in the definition of "human subject" to include biospecimens as proposed, and not either of the two narrower and convoluted alternative proposals. A consistent problem in the NPRM is its level of complexity, and the fact that the preamble often does not seem to match up with the regulatory text.

ACP supports informed consent for all uses, storage, maintenance and secondary research use of biospecimens *and* identifiable information, especially genomic data. These materials and information are not only about the individual, but also about the individual's family.

The NPRM's proposed "broad consent" needs refinement so that it not so broad, but it may contain a workable approach. Other approaches, such as a notice of research practices combined with an opt-out procedure (as SACHRP has recommended) are insufficiently protective of subject rights and welfare, as are Alternative Proposals A and B of the NPRM. As the NPRM itself recognizes, it is difficult if not impossible to make biospecimens non-identified and "a number of reports have already demonstrated the ability to re-identify individuals from biospecimens or data that lack direct identifiers." Beneficence, and respect for persons and for autonomy, in addition to the growing literature on patient/subject preferences about how their materials and information are used (and not used based on potential objections to certain kinds of research), requires the opportunity for consent or refusal of consent. The critical lessons of the Henrietta Lacks and Havasupai tribe cases about the necessity of respect for the rights and the welfare of human subjects need to be reflected in changes to the Common Rule and unfortunately, are not, under the NPRM.

ACP policy asserts that research with human biological materials has implications for the privacy of research subjects and individuals with a genetic relationship to research subjects. Fully informed and transparent consent requires the disclosure of all potential uses of patient/subject data. The consent process needs to include the desired preferences of research subjects regarding future contact for notification about results and/or consent for additional research participation. Research should be limited to the use specified during the informed consent process. Communication of the risks and benefits of research involving biological material allows research subjects to make a well-informed decision.

Further study is needed to resolve informed consent issues related to future research use, including biologic materials. ACP supports the 2009 Institute of Medicine (IOM) report, Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research recommendation allowing future use of existing materials for research if the following conditions are met: "(1) the individual's authorization describes the types or categories of research that may be conducted with the PHI stored in the database or biobank; and (2) an IRB determines that the proposed new research is not incompatible with the initial consent and authorization, and poses no more than a minimal risk."

The term "broad consent" is used in the NPRM. "Broad consent" is not ethically meaningful. But the provisions in the proposed regulatory text could be made more meaningful if they were to be refined further. The NPRM regulatory text says in pertinent part that "(c)(1) Elements of

informed consent for broad consent to the storage, maintenance, and secondary research use of biospecimens or identifiable private information should include: (i) A general description of the types of research that may be conducted with information and biospecimens and the information that is expected to be generated from the research, the types of information or biospecimens that might be used in research, and the types of institutions that might conduct research with the biospecimens or information…"

Many potential subjects, however, would only consent to use of their biospecimens or information for research on a particular disease-- say, cancer research-- or even more specifically, breast cancer research (and many might strongly object to uses other than those specifically enumerated, as did the Havasupai tribe). In the provision above, "A general description" should be changed to something along the lines of: *A description of the types or categories of research such as a disease category (ie, cancer) or specific disease (ie, breast cancer) that may be conducted...*. This would allow for more meaningful consent when implemented along with the other provisions of this section.

Single IRB and Streamlining IRB Review of Multi-Site Studies

ACP supports the proposal that all domestic sites in a multi-site study use a single IRB as the IRB of record, chosen by the funder to help safeguard against IRB-shopping. If workable, this might help lessen delays in research. However, criteria for how the IRB is to be chosen need to be established and there needs to be a robust mechanism for engagement and input by local IRBs based on local perspectives, laws, training requirements and community consultation. Guidelines on how to accomplish this are needed.

Improving Informed Consent

ACP supports more emphasis on the process, not just documentation, of informed consent. We support the proposed simplifications and refocusing of informed consent documents with guidance for clearly defined information. However, ACP has concerns about the proposed consent process for biospecimens and identifiable information in research as noted above.

Data Collection to Enhance System Oversight

ACP supports establishment of an electronic reporting system for adverse events and is disappointed this has been removed from the NPRM.

Extension of Federal Regulations

ACP supports extending the Common Rule to all clinical trials conducted at US institutions that are federally funded for human subjects research.

Final Comments:

Throughout the NPRM the terms "subjects" and "participants" are both used, while the Common Rule uses subjects to refer to those who volunteer for research. We urge that any changes to the Common rule also use the term "subjects." This is a deliberate choice of language. Some argue "participant" is more respectful of research volunteers. But it is actually more respectful and honest to recognize that individuals who volunteer for research will not

necessarily benefit from the research. They should not be identified with a passive term such as participants. "Subjects" recognizes the power and knowledge imbalance between investigators conducting the research and individuals on whom the research is conducted, and makes clearer the need for regulations and processes to help ensure respect, and protection, for those who volunteer.

We were also concerned to learn that most of the 1051 comments on the ANPRM were received from investigators and urge that HHS make a concerted effort to solicit more input from subjects, research ethicists and the research protections community for a more balanced approach. Also, as ethics is not a matter of majority opinion, we would hope that the many summaries of the "majority of comments" throughout the NPRM do not necessarily represent the direction of the final rule. We hope that attention to ethical concerns will be heightened above concerns about efficiencies in research.

Thank you for the opportunity to comment on the notice of proposed rulemaking on human subjects research protections. We hope these comments are of assistance. If you have any questions, please feel free to contact Lois Snyder Sulmasy, JD, Director of ACP's Center for Ethics and Professionalism at 215/351-2835 or lsnyder@acponline.org.

Sincerely,

Wayne J. Riley, MD, MPH, MBA, MACP
President, American College of Physicians

cc: Lois Snyder Sulmasy, JD