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January 6, 2016

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: Federal Policy for the Protection of Human Subjects; Proposed Rules (Docket number HHS-OPHS-2015-0008)

Dear Dr. Menikoff:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, offers the following comments regarding the September 8, 2015, notice of proposed rulemaking (NPRM) that would amend the Federal Policy for the Protection of Human Subjects (hereafter referred to as the Common Rule).

A. General Comments

(1) The NPRM would transform the Common Rule — which is currently written in clear, concise, and, in most respects, easily understood language — into a document that is exceedingly confusing, overly complex, and written in very opaque language in multiple sections. This confusion is most apparent in the newly created categories of activities that would be excluded from the policy, the revised categories of exempt human subjects research, and the numerous provisions related to research with biospecimens that are scattered throughout multiple sections of the proposed revision to the Common Rule. Particularly frustrating is the intricate relationships and numerous cross-references between multiple elements of the proposed rule.

(2) 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.

(3) 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.

(4) In light of our first three comments, we agree with the following recommendations of the Secretary's Advisory Committee on Human Research Protections (SACHRP):[1]

(a) SACHRP recommends that the Department of Health and Human Services (HHS) conduct a comprehensive rewrite 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, institutional review board (IRB) professionals, sponsors and other experts.

(b) Prior to the publication of final rules, SACHRP supports a second publication of an NPRM that presents a simplified, focused set of proposals for further public consideration and comment.

(5) Throughout the NPRM's preamble, there are multiple uses of the term "participants" when referring to "human subjects." We believe the regulatory term "human subject" should be used throughout the preamble of any subsequent NPRM or final rule because (a) the term "participants" fails to capture the uniquely vulnerable status of human subjects involved in research relative to the many other people who participate in human subjects research study, such as investigators and sponsors; and (b) this would align the preamble discussion with the terminology in the actual regulatory text.

(6) We generally support adding new requirements for research involving biospecimens, regardless of identifiability, that come from living individuals and that were originally collected for some other purpose in a research or non-research setting. However, to avoid the confusion caused by numerous biospecimen research provisions scattered throughout multiple sections of the proposed rule, the Common Rule departments and agencies should consider creating a separate subpart that addresses only research involving biospecimens.

B. Specific Comments and Responses to Selected Questions

We have the following comments about specific proposed provisions and responses to some of the questions posed in the NPRM:

(1) In question 1, the NPRM asks: *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.*

As noted in our comment A(1) above, the proposed revisions to the Common Rule are exceedingly confusing, overly complex, and written in very opaque language. As a result,

[1] Secretary's Advisory Committee on Human Research Protections. Recommendations on the notice of proposed rulemaking entitled "Federal Policy for the Protection of Human Subjects." http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2015-0008-0570. Accessed January 5, 2016.

the proposed changes would significantly increase, not decrease, regulatory ambiguity for investigators, institutions, IRBs, human subjects, and human subject advocates.

Moreover, while the proposed rules would add additional protections for human subjects involved in minimal-risk research involving biospecimens, they would do little to strengthen the protections for human subjects involved in greater-than-minimal-risk research, such as clinical trials, which clearly pose the greatest risks of harm to subjects. As recent history has shown — take, for example, the serious widespread IRB failures related to the reviews of the Surfactant, Positive Airway Pressure, and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) trial;[2,3] the Transfusion of Prematures (TOP) Trial;[4] the Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) Trial;[5] and the Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Trial[6] — the system for protecting human subjects in the U.S. appears to be broken. IRBs routinely lack appropriate expertise among their members to adequately assess the design, risks, benefits, and informed-consent procedures for high-risk research studies, and even if they have such expertise, IRBs too often fail to raise important questions regarding these issues.

The NPRM, like the 2011 advance notice of proposed rulemaking,[7] appears to be premised on the assumption that reducing the time and effort IRBs spend reviewing certain minimal-risk research (i.e., decreasing protections for subjects participating in minimal-risk research) will allow IRBs to spend more time and effort reviewing greater-than-minimal-risk research, thus enhancing protections for subjects enrolled in such research. However, the Common Rule departments and agencies offer no evidence that this will be the result if the NPRM were to be implemented as written. It is very likely that if the NPRM proposals are implemented in a final rule without additional specific requirements for greater-than-minimal-risk research, many IRBs, already feeling overburdened, will not take steps to improve the expertise among their members and the quality of their reviews and will simply spend the same amount of time and effort

[2] Public Citizen. Report Prepared for Secretary of Health and Human Services Kathleen Sebelius: Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure That Risks Were Minimized. https://www.citizen.org/hrg2124. Accessed January 5, 2016.
[3] Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf. Accessed January 5, 2016.
[4] Public Citizen. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the Tranfusion of Prematures (TOP) trial. August 22, 2013. http://www.citizen.org/documents/2150.pdf. Accessed January 6, 2016.
[5] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the Flexibility in Duty Hour Requirements for Surgical Trainees (FIRST) Trial. November 19, 2015. http://www.citizen.org/documents/2284.pdf. Accessed January 6, 2016.
[6] Public Citizen and the American Medical Student Association. Letter to the Office for Human Research Protections regarding the Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education (iCOMPARE) Trial. November 19, 2015. http://www.citizen.org/documents/2283.pdf. Accessed January 6, 2016.
[7] 76 FR 44512.

reviewing greater-than-minimal-risk research as they currently spend, resulting in no enhanced protections for subjects participating in such research.

The Common Rule should include additional provisions to ensure that IRB members have appropriate knowledge and expertise regarding the research reviewed by the IRB, and that, prior to its reviews, investigators provide the IRB with all relevant information regarding the interventions to be studied in proposed research studies. Too often, IRB members lack up-to-date knowledge and relevant expertise necessary for the IRB to make the determinations required for approval of research under Section __.111. Likewise, investigators frequently withhold information that is relevant to these determinations and that might lead the IRB to disapprove the research or require substantial changes as a condition of approval. As a result, human subjects are frequently enrolled in research that is unethical and places them at risk of unnecessary harm. For example, IRBs frequently approve research that involves inappropriate randomization of subjects who have serious illnesses to placebo groups that are denied standard treatments proven to be effective.

One basic step to strengthen protections for human subjects would be to expand Section __.108 (IRB functions and operations) to include a provision stating that when research is reviewed by the IRB at a convened meeting, (a) IRB members with sufficient professional background and expertise necessary to ensure adequate review of the research must attend the meeting and participate in the review; or (b) individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB must be invited to attend the meeting and must participate to ensure adequate review of the research.

We also urge HHS and the other Common Rule departments and agencies to add new provisions in the Common Rule that would finally implement the following important recommendations made by the National Bioethics Advisory Commission in 2001:[8]

> Recommendation 3.1: All institutions and sponsors engaged in research involving human participants should provide educational programs in research ethics to appropriate institutional officials, investigators, IRB members, and IRB staff. Among other issues, these programs should emphasize the obligations of institutions, sponsors, IRBs, and investigators to protect the rights and welfare of participants.
>
> Recommendation 3.3: All investigators, IRB members, and IRB staff should be certified prior to conducting or reviewing research involving human participants. Certification requirements should be appropriate to their roles and to the area of research. Federal policy should set standards for determining whether institutions and sponsors have an effective process of certification in place.

[8] National Bioethics Advisory Commission. Ethical and Policy Issues in Research Involving Human Participants: Volume 1 – Report and Recommendations of the National Bioethics Advisory Commission. August 2001. Available at http://bioethics.georgetown.edu/nbac/human/overvol1.pdf. Accessed December 21, 2011.

Recommendation 3.7: Federal policy should define institutional, IRB, and investigator conflicts of interest.

Recommendation 3.9: Federal policy should establish standards and criteria for the selection of IRB members. The distribution of IRB members with relevant expertise and experience should be commensurate with the types of research reviewed by the IRB.

Recommendation 3.10: IRBs should include members who represent the perspectives of human subjects, members who are unaffiliated with the institution, and members whose primary concerns are in nonscientific areas. An individual can fulfill one, two, or all three of these categories. For the purposes of both overall membership and quorum determinations (a) these persons should collectively represent at least 25 percent of the IRB membership; and (b) members from all of these categories should be represented each time an IRB meets.

Recommendation 4.1: An analysis of the risks and potential benefits of study components should be applied to all types of covered research. In general, each component of a study should be evaluated separately, and its risks should be both reasonable in themselves as well as justified by the potential benefits to society or the human subjects. Potential benefits from one component of a study should not be used to justify risks posed by a separate component of a study.

Recommendation 6.1: Federal policy should describe how sponsors, institutions, and investigators should monitor ongoing research.

(2) Proposed Section __.101(a)(2) would extend applicability of the Common Rule to all clinical trials, irrespective of funding source, that meet all of the following conditions:

(a) The clinical trials are conducted by an institution that receives support from a Federal department or agency for human subjects research that is not excluded from this policy under [proposed] Section __.101(b)(2) and does not qualify for exemption in accordance with [proposed] Section __.104;
(b) The clinical trials are not subject to regulation by the Food and Drug Administration (FDA); and
(c) The clinical trials are conducted at an institution located within the U.S.

We strongly support this provision in general, but oppose limiting it to clinical trials. Applicability of the Common Rule should be expanded to any non-excluded, non-exempt human subjects research.

(3) Proposed Section __.102(b)(1)(i) would exclude from coverage under the Common Rule activities that involve data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purpose other than the currently proposed activity, or is obtained

through oral or written communications with individuals (e.g., surveys or interviews). These activities would be excluded because "they will be deemed not to involve research." We find the language describing this exclusion category to be unclear and are concerned that this ambiguity to lead to misapplying this exclusion to activities that do constitute human subjects research. We recommend eliminating this exclusion provision from any final rule.

(4) In question 6, the NPRM asks: *Public comment is sought for whether this excluded activity [described in Section __.102(b)(1)(i)] should simply be discussed in the text of the final rule's preamble, and guidance produced to assist investigators in making such a determination, or whether any other similar exclusions should be addressed.*

This question is very unclear.

(5) Proposed Section __.102(b)(1)(iv) would exclude from coverage under the Common Rule the following:

> Quality assurance or improvement activities involving the implementation of an accepted practice to improve the delivery or quality of care or services (including, but not limited to, education, training, and changing procedures related to care or services) if the purposes are limited to altering the utilization of the accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. This exclusion does not cover the evaluation of an accepted practice itself.

These activities would be excluded because "they will be deemed not to involve research."

We oppose this exclusion category because the language is ambiguous and, as a result, there is a high likelihood this exclusion will be misapplied to many activities that involve human subjects research and should be subject to the Common Rule's IRB review and informed consent requirements. For example, had proposed Section __.102(b)(1)(iv) been a provision of the current Common Rule, it is likely that the researchers conducting the unethical iCOMPARE Trial and FIRST Trial would have declared these trials to be excluded under this provision.

We also are aware that the Office for Human Research Protections (OHRP) for years has expressed serious concerns to the senior leadership of HHS that many HHS agencies, including the FDA, the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services, and the Substance Abuse and Mental Health Services Administration (SAMHSA), among others, repeatedly skirted the HHS regulations for the protection of human subjects by incorrectly determining that many activities conducted or supported by these agencies did not meet the definition of human subjects research or qualified for an exemption. Many of these activities involved non-exempt human subjects research in the areas of public health, quality improvement, and program evaluation. The agency officials making these incorrect determinations frequently had conflicts of interest and were interested in reducing the regulatory burdens

faced by their intramural or extramural researchers. For example, SAMHSA officials have repeatedly asserted that many research studies testing interventions for treating drug abuse did not involve non-exempt human subjects research, when in fact OHRP concluded otherwise.

Section __.101(d) of the current Common Rule (and proposed Section __.102(l) of the NPRM) defines *research* as follows:

> *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Given this definition, the scope of activities covered by the Common Rule clearly was intended to be broad, and many public health, quality improvement, and program evaluation activities meet this definition, involve human subjects, and do not qualify — no should they qualify — for any current exemption. More importantly, many quality improvement and public health activities that meet the current definition of research involve interactions or interventions with human subjects that pose risks to subjects. In addition, many quality improvement research activities involve manipulation of patients' medical care for research purposes in order to test a hypothesis or answer a scientific question.

Indeed, the following statement in the preamble of the NPRM regarding proposed Section __.102(b)(1)(iv) appears to directly contradict the assertion that the relevant activities are not research:

> These efforts, some of which could be judged to be research, should be carried out because of the recognized public good they achieve. This exclusion is intended to avoid impeding such efforts where the Common Rule's requirements might have a chilling effect on the ability to learn from, and conduct, important types of innovation.

Therefore, we urge that proposed Section __.102(b)(1)(iv) not be included in any final rule amending the Common Rule. However, in the event this section is retained in any final rule, we urge that this provision be revised to eliminate ambiguity. One way to accomplish this would be to expand the actual regulatory text to include the following statements from the preamble:

> [T]his exclusion does not include evaluations of different accepted practices themselves, however, such as activities designed to determine whether a particular accepted medical treatment is or is not more effective than another. …

> This does not include quality improvement activities designed with a research purpose relating to the safety and efficacy of the accepted practice. It is accordingly important to note that activities that *do* involve such research—for example, assigning patients to different versions of treatments that are within the standard of care in order to evaluate the differences between those treatments in terms of effectiveness or risks—would not come within this exclusion.

(6) Proposed Section __.102(b)(1)(v) would exclude from coverage under the Common Rule the following:

> Public health surveillance activities, including the collection and testing of biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority and limited to those necessary to allow the public health authority to identify, monitor, assess, or investigate potential public health signals or the onset of a disease outbreak, including trends, or signals, and patterns in diseases, or a sudden increase in injuries from using a consumer product, or conditions of public health importance, from data, and including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made disasters.

We oppose this exclusion category because the scope of this exclusion is too broad, excluding from coverage under the Common Rule a large body of epidemiology research involving human subjects that is conducted or funded by the National Institutes of Health and the CDC. (See also our preceding comments.)

(7) Proposed Section __.101(b)(2) would exclude from coverage under the Common Rule four categories of low-risk human subjects research. Several of these research activities would qualify for one of the exemptions under Section __.101(b) of the current Common Rule. We recommend that each of these categories of human subjects research be placed in the section of the proposed rule that would include exemptions (Section __.104) and that someone other than the investigators be required to determine independently whether the research indeed meets the criteria defining these categories.

(8) In question 9, the NPRM asks: *Public comment is requested on the extent to which covering any of these activities [described in Section __.101(b)(2)(i)] under the Common Rule would substantially add to the protections provided to human research subjects.*

The category includes research involving survey procedures, interview procedures, or observation of public behavior. When such research involves investigators collecting information that may be damaging to the subjects' financial standing, employability, educational advancement, or reputation if disclosed, it should be covered by the Common Rule to ensure that the investigators have implemented appropriate safeguards to protect the confidentiality of the collected information.

(9) In question 10, the NPRM asks: *Public comment is sought on whether this exclusion [described in Section __.101(b)(2)(i)] should only apply to research activities in which*

notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, please comment on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, ability to opt-out, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?

We note that the last sentence of this question incorrectly refers to this proposed category of research as "exempt." Whether this category of research is maintained in the section on exclusions or moved to the section on exemptions as we recommend, the regulations should require that notice about the research be given to the prospective subjects or their legally authorized representatives. The notice should include the purpose of the research, a description of the privacy safeguards, and a statement that participation is voluntary and that the subjects may opt out or end their participation at any time. In considering the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

(10) In question 11, the NPRM asks: *Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category [described in Section __.101(b)(2)(i)]. If so, should documentation of any kind be generated and retained?*

No, it would not be reasonable to rely on investigators to make self-determinations about whether such research meets the criteria for the proposed exclusion category and is covered under the Common Rule. As OHRP is well aware from its compliance oversight activities, investigators — who have an obvious conflict of interest — often err in making determinations about whether research meets the criteria for the current exemption categories.

(11) In question 13, the NPRM asks: *Public comment is sought regarding whether these exclusions [described in Section __.101(b)(2)(i)] should be narrowed such that studies with the potential for psychological risk are not included.*

If this category of research is maintained as an exclusion in any final rule, it should be narrowed such that studies with the potential for psychological risk are not included in this category.

(12) In question 14, the NPRM asks: *For activities captured under the third element of this exclusion [described in Section __.101(b)(2)(i)], do the statutory, regulatory, and other policy requirements cited provide enough oversight and protection that being subject to expedited review under the Common Rule would produce minimal additional subject protections? If so, should the exclusion be broadened to also cover secondary analysis of information collected pursuant to such activities?*

No, the third element of this exclusion — i.e., that the research will involve a collection of information subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.;* research information will be maintained on information technology that is subject to and

in compliance with section 208(b) of the EGovernment Act of 2002, 44 U.S.C. 3501 note; and all of the information collected, used, or generated as part of the research will be maintained in a system or systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a — fails to provide sufficient oversight and protection, and this exclusion, if included in any final rule, should not be broadened to also cover secondary analyses of information collected pursuant to such activities. As the recent breaches of highly sensitive records maintained by the Office of Personnel Management and the Internal Revenue Service have demonstrated, the Paperwork Reduction Act of 1995, the EGovernment Act of 2002, and the Privacy Act of 1974 provide flimsy protections at best.

(13) In question 16, the NPRM asks: *Public comment is sought regarding whether it is reasonable to rely on investigators to make self-determinations for the types of research activities covered in this particular exclusion category [described in Section __.101(b)(2)(ii)]. If so, should documentation of any kind be generated and retained?*

No, it would not be reasonable to rely on investigators to make self-determinations about whether such research meets the criteria for the proposed exclusion category and is covered under the Common Rule. As OHRP is well aware from its compliance oversight activities, investigators — who have an obvious conflict of interest — often err in making determinations about whether research meets the criteria for the current exemption categories.

(14) The NPRM proposes to amend Section __.101(c) of the Common Rule to read as follows (new text in bold):

> Department or agency heads retain final judgment as to whether a particular activity is covered by this policy, **which judgment shall be exercised consistent with the ethical principles of the Belmont Report**.

We strongly support the proposed revisions.

(15) The NPRM proposes to amend Section __.101(i) of the Common Rule to read as follows (new text in bold):

> Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy **provided the alternative procedures to be followed are consistent with the principles of the Belmont Report**. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, or to the equivalent office within the appropriate Federal department or agency, and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures. **The waiver notice must include a statement that identifies the conditions under which the**

waiver will be applied and a justification as to why the waiver is appropriate for the research, including how the decision is consistent with the principles in Belmont Report. Each Federal department or agency conducting or supporting the research must establish, on a publicly accessible federal Web site, a list of the research for which a waiver has been issued.

We strongly support the proposed revisions.

(16) Section __.102(e) of the proposed rule would revise the definition of *human subject* to read as follows:

> (e)(1) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:
> (i) Obtains data through intervention or interaction with the individual, and uses, studies, or analyzes the data;
> (ii) Obtains, uses, studies, analyzes, or generates identifiable private information; or (iii) Obtains, uses, studies, or analyzes biospecimens.
> (2) Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
> (3) Interaction includes communication or interpersonal contact between investigator and subject.
> (4) Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be shared or made public (e.g., a medical record or clinically obtained biospecimen).
> (5) Identifiable private information is private information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

Proposed Section __.102(e)(1) of this definition is sloppily written, contains significant inconsistencies, and is very confusing, in contrast to the definition of *human subject* under the current Common Rule. First, under proposed Section __.102(e)(1)(i), the data obtained through intervention or interaction with a living individual must be used, studied, or analyzed in order for that individual to be a human subject. In contrast, under proposed Sections __.102(e)(1)(ii) and (iii), when an investigator obtains either identifiable private information about a living individual or a biospecimen that comes from a living individual, that individual would be a human subject, even if the identifiable private information or biospecimen is not used, studied, or analyzed. To resolve this confusion, we recommend that the phrase "and uses, studies, or analyzes the data" be deleted from Section __.102(e)(1)(i). We further recommend that the phrase "uses, studies, analyzes" be deleted from Section __.102(e)(1)(ii).

Second, the grammatical structure of the introductory text in Section __.102(e)(1) combined with Section __.102(e)(1)(iii) is nonsensical. In particular, an investigator does

not obtain, use study, or analyze a biospecimen *about* a living individual. Better phrasing might be "a biospecimen that comes from a living individual." Such rephrasing would require reorganizing Section __.102(e)(1).

(17) The NPRM proposes to delete the following provision found in Section __.103(b) of the current Common Rule:

> Assurances applicable to federally supported or conducted research shall at a minimum include:
> (1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §__.101(b) or (i).

The preamble to the NPRM offers the following rationale for this change to the assurance requirements:

> This change was made because this provision is generally not enforced. Further, for international institutions that may receive U.S. government funding for research activities, it creates the impression that these international institutions must modify their internal procedures to comport with the set of principles designated on the FWA for activities conducted at those institutions that receive no U.S. government funding. OHRP specifically has received many questions about the extent to which international institutions must adhere to the ethical principles designated as part of the assurance process in research activities conducted by the institution that receive no Common Rule department or agency funding. In order to provide clarity to these international institutions that such measures are not required, the NPRM proposes to delete the requirement at §__.103(b)(1).

We oppose the elimination of this provision from the Common Rule because the provision appropriately emphasizes to institutions that the protection of human subjects is founded on fundamental ethical principles.

Moreover, the rationale for eliminating this provision is woefully insufficient. First, it is not true that this provision of the regulations is generally not enforced. The current Federalwide Assurance (FWA), which is required for all HHS-funded research and is relied upon by most of the other Common Rule departments and agencies, contains a statement of principles as a required element. Thus, the provision under Section __.103(b)(1) is enforced uniformly for all FWA-holding institutions.

Second, the provision under Section __.103(b)(1) and the current FWA provide non-U.S. institutions with great flexibility in choosing a statement of principles, which should

minimize the need for these institutions to modify their internal procedures to comport with the set of principles designated in the FWA for human subjects research activities not funded by the U.S. government. But even if this were a legitimate concern, a much better solution would be to simply modify the provision as follows, rather than completely eliminating it (recommended changes in bold):

> (1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research **~~conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation~~to which the assurance applies**. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research **~~and need not be applicable to any research exempted or waived under §__.101(b) or (i)~~**.

(18) The NPRM proposes to add a new Section __.103(e) stating the following:

> (e) For non-exempt research involving human subjects covered by this policy that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall establish and follow procedures for documenting the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy.

We support this new provision in general, but note that limiting it to "non-exempt research" appears to be too narrow a restriction, as some categories of exempt research require some limited IRB review, which might be conducted by an IRB that is not operated by the institution. We suggest the following revision (recommended changes in bold):

> (e) For **~~non-exempt~~** research involving human subjects covered by this policy**, with the exception of research excluded by this policy under §__.101(b) or eligible for exemption under §__.104(d),** that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall establish and follow procedures for documenting the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy.

(19) Proposed Section __.104(c) would allow investigators to independently determine that their own research qualifies for one of the exempt categories of research using decision tools to be developed by Common Rule departments and agencies. We oppose this provision. It would not be reasonable to rely on investigators to make self-determinations about whether research meets the criteria for the proposed exemption categories. As OHRP is well aware from its compliance oversight activities, investigators — who have

an obvious conflict of interest — often err in making determinations about whether research meets the criteria for the current exemption categories. Any decision tool could be undermined easily by failure to input complete and accurate information about the proposed research. Therefore, someone other than the investigator who has access to the complete research protocol should make exemption determinations.

(20) In question 32, the NPRM asks: *Public comment is sought regarding what additional information should be required to be kept as a record other than the information submitted into the decision tool, for example, a study abstract, the privacy safeguards to be employed, or any notice or consent document that will be provided.*

For research determined to be exempt, institutions should be required to keep the complete research protocol, subsequent modifications of the protocol, a description of privacy safeguards, and any notice or consent documents that will be provided to subjects.

(21) In question 33, the NPRM asks: *Public comment is sought regarding the value of adding an auditing requirement [for exemption determinations made by investigators using decision tools to be developed by Common Rule departments and agencies]*.

If any final rule includes provisions allowing investigators to independently determine whether their own research is exempt under the Common Rule, the regulations should include an additional requirement that institutions audit all such determinations.

(22) The NPRM proposes to add a new Section __.104(d) stating the following:

> (d) The following categories of exempt human subjects research generally involve a low-risk intervention with human subjects, must be recorded as required in paragraph (c) of this section, and do not require application of standards for information and biospecimen protection provided in Sec. __.105 or informed consent. Only paragraph (d)(2) of this section allows for the collection and use of biospecimens.

It is unclear what "low-risk" means. Does it have the same meaning as "minimal risk?" If so, "low-risk" should be changed to "minimal-risk." Otherwise, "low-risk" should be defined.

It also is unclear whether research that would otherwise meet the criteria for the exemption categories under proposed Section __.104(d) but that would involve interventions presenting a level of risk greater than "low" would qualify for the exemptions. We would oppose application of these exemptions to research involving greater than minimal risk to subjects.

(23) The first exemption under proposed Section __.104(d) would be:

> (1) Research conducted in established or commonly accepted educational settings when it specifically involves normal educational practices. This includes most

> research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods that are not likely to adversely impact students' opportunity to learn required educational content in that educational setting or the assessment of educators who provide instruction.

The inclusion of the word "most" in the second sentence creates unnecessary ambiguity. We recommend the following revisions to this sentence (recommend changes in bold):

> This includes **~~most~~** research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods**, provided** that **~~are~~the research is** not likely to adversely impact students' opportunity to learn required educational content in that educational setting or the assessment of educators who provide instruction.

(24) In question 34, the NPRM asks: *Public comment is sought on whether this exemption category [described in Section __.104(d)(1)] should only apply to research activities in which notice that the information collected will be used for research purposes is given to prospective subjects or their legally authorized representatives as a regulatory requirement, when not already required under the Privacy Act of 1974. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose, privacy safeguards, contact information, etc. Comment is also sought on how such a notice should be delivered, e.g., publication in a newspaper or posting in a public place such as the school where the research is taking place, or by individual email or postal delivery. Note that other requirements, such as those of the Family Educational Rights and Privacy Act (FERPA) or the Protection of Pupil Rights Amendment, may also apply. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?*

The proposed exemption at Section __.104(d)(1) should apply only to research activities in which notice that the information collected will be used for research purposes is given to prospective subjects or their legally authorized representatives as a regulatory requirement. The notice should include the purpose and nature of the research, a description of the privacy safeguards, contact information for where to obtain additional information about the research, and a statement that participation is voluntary and that the subjects may opt out or end their participation at any time. This notice should be communicated by individual email or postal delivery to each subject or each subject's legally authorized representative. In considering such notices and the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

(25) In question 35, the NPRM asks: *Public comment is sought on whether the privacy safeguards of Sec. __.105 should apply to the research included in Sec. __.104(d)(1), given that such research may involve risk of disclosure of identifiable private information.*

Yes, the privacy safeguards of Section __.105 should apply to research qualifying for the exemption under proposed Section __.104(d)(1).

(26) In question 36, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(d)(2)] should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, e.g., the research purpose, privacy safeguards, or contact information. Also comment on how such a notice should be delivered; e.g., publication in a newspaper or posting in a public place, or by individual email or postal delivery. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? In many cases, it may be that individual notice or consent to all potentially affected persons before the research or demonstration commences is ordinarily impossible in the conduct of such studies. For example, if a research or demonstration project will affect all inhabitants of a large geographic area (e.g., a housing, a police patrol, a traffic control, or emergency response experiment), or all clients or employees of a particular program or organization or setting will be subject to a new procedure being tested (e.g. a new approach to improving student performance, a new anti-smoking or anti-obesity program, a new method for evaluating employee performance), would it be possible to make participation voluntary for all affected individuals, or even to identify and inform all affected individuals in advance?*

The proposed exemption at Section __.104(d)(2) should apply only to research activities in which notice about the research is given to the prospective subjects or their legally authorized representatives as a regulatory requirement. The notice should include the purpose and nature of the research, a description of the privacy safeguards, and contact information for where to obtain additional information about the research. This notice should be communicated by individual email or postal delivery to each subject or each subject's legally authorized representative. In considering such notices and the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

For a research or demonstration project that would affect all inhabitants of a large geographic area or would involve subjecting all clients or employees of a particular program or organization to a new procedure being tested, it obviously would be impossible to make participation voluntary for all affected individuals. In such cases, the research should not qualify for the exemption under Section __.104(d)(2) and should undergo review by an IRB. Whenever feasible, there should be transparency about the research for the subjects.

(27) In question 37, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(d)(2)] is appropriate based on the recognition that alternative processes are in place in which ethical issues raised by research in public benefit or service programs would be addressed by the officials who are familiar with the programs and responsible for their successful operation under state and federal*

laws, rather than meeting specific risk-based criteria, or whether risk limitations should be included, and if so, what those limitations should be. Though long-standing, this exemption has never identified specific risk-based criteria, or risk limitations to bound the type of projects that may be covered. When originally promulgated, the exemption did stipulate that following the review of such projects, if the Secretary determines that the research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject, then written informed consent would be required. Public comment is sought on whether to limit the risk that can be imposed on subjects while using this exemption, and if so, how to characterize those limits in a clear fashion. If more than minimal risk interventions are included, public comment is sought on whether, for transparency, this should be made clear in the regulatory text.

There should be a risk limit placed on research that would qualify for exemption under Section __.104(d)(2): Such research should involve no more than minimal risk. Public officials cannot be trusted always to make appropriate ethical decisions regarding research in public benefit or service programs. For research involving more than minimal risk, IRB review and the informed consent of the subjects should be required.

(28) The exemption category proposed under Section __.104(d)(3) of the NPRM would cover certain research involving benign interventions in conjunction with the collection of data from adult subjects through verbal or written responses or video recording if the subject prospectively agrees to the intervention and data collection. This exemption would not apply to research that involves deceiving the subjects regarding the nature or purpose of the research *unless* the subject authorizes the deception. Authorized deception would mean the subjects prospectively agree to participate in the research where the subjects are informed they will be unaware or misled regarding the nature or purposes of the research.

We agree that for research qualifying for exemption under Section __.104(d)(3), deception should not be allowed unless the subjects authorize the deception. We recommend that this exemption include additional provisions requiring that investigators (a) disclose to the subjects the actual nature and purpose of the research after the subject's participation ends; and (b) following this disclosure, give subjects the option of having their data be excluded from further use or analysis by the investigators.

(29) In question 39, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(d)(3)] should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice, such as the research purpose (if authorized deception is not utilized), privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence?*

The proposed exemption at Section __.104(d)(3) of the NPRM should apply only to research activities in which notice about the research is given to prospective subjects or their legally authorized representatives as a regulatory requirement. The notice should

include the purpose and nature of the research (unless deception is involved; see our preceding comment), a description of the privacy safeguards, contact information for where to obtain additional information about the research, and a statement that participation is voluntary and that the subjects may opt out or end their participation at any time. In considering such notices and the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

(30) In question 41, the NPRM asks: *Public comment is sought on whether it is reasonable, for purposes of this exemption [described at Section __.104(d)(3)], to rely on the exemption determination produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances.*

No, it would not be reasonable to rely on investigators to make self-determinations about whether research meets the criteria for the proposed exemption category under Section __.104(d)(3) of the NPRM. As OHRP is well aware from its compliance oversight activities, investigators — who have an obvious conflict of interest — often err in making determinations about whether research meets the criteria for the current exemption categories. Any decision tool could be undermined easily by failure to input complete and accurate information about the proposed research. Therefore, someone other than the investigator who has access to the complete research protocol should make exemption determinations.

(31) In question 42, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(d)(4) and involving taste and food quality evaluation and certain consumer acceptance studies of foods] should be narrowed to apply only to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? Should prospective subjects be given the explicit opportunity to opt out of such research?*

The proposed exemption at Section __.104(d)(4) of the NPRM should apply only to research activities in which notice about the research is given to prospective subjects or their legally authorized representatives as a regulatory requirement. The notice should include the purpose and nature of the research, a description of the privacy safeguards, contact information for where to obtain additional information about the research, and a statement that participation is voluntary and that the subjects may opt out or end their participation at any time. In considering such notices and the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

(32) The NPRM proposes to add a new Section __.104(e) stating the following:

> The following categories of exempt human subjects research allow for the collection of sensitive information about human subjects, must not involve biospecimens, must be recorded as required in paragraph (c) of this section, and require application of standards for information and biospecimen protection provided in Sec. __.105

The term "sensitive information" is ambiguous. Does this mean information that would reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation? Does it include other types of information? This term should be defined in the regulations.

(33) The first exemption category under Section __.104(e) of the NPRM would be:

> (1) Research, not including interventions, involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording), if the information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects.

We oppose including this category of research within the exemptions under Section __.104.

(34) In question 45, the NPRM asks: *Public comment is sought on whether the proposed exemption [described at Section __.104(e)(1)] regarding the use of educational tests, survey procedures, interview procedures, or observation of public behavior (Sec. __.104(e)(1)) should be applied to research involving the use of educational tests with children and whether it should also be applied to research involving the use of survey or interview procedures with children. If so, for research involving children, should the permissible survey or interview topics be limited in some way?*

If the proposed exemption at Section __.104(e)(1) is included in any final rule, it should not apply to research involving children.

(35) In question 46, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(e)(1)] should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement. If so, comment is sought on what kind of information should be included in the notice such as the research purpose, privacy safeguards, contact information, etc. Would requiring notice as a condition of this exempt research strike a good balance between autonomy and beneficence? Should prospective subjects be given the explicit opportunity to opt out of such research?*

If the proposed exemption at Section __.104(e)(1) is included in any final rule, it should apply only to research activities in which notice about the research is given to prospective

subjects or their legally authorized representatives as a regulatory requirement. The notice should include the purpose and nature of the research, a description of the privacy safeguards, contact information for where to obtain additional information about the research, and a statement that participation is voluntary and that the subjects may opt out or end their participation at any time. In considering such notices and the balance between autonomy and beneficence, we believe greater weight should be given to the principle of respect for persons and the promotion of subject autonomy.

(36) In question 47, the NPRM asks: *Public comment is sought on whether it is reasonable, for purposes of this exemption [described at Section __.104(e)(1)], to rely on the exemption determinations produced by the decision tool where investigators themselves input the data into the tool, or whether there should be further administrative review in such circumstances?*

No, if the proposed exemption at Section __.104(e)(1) is included in any final rule, it would not be reasonable to rely on investigators to make self-determinations about whether research meets the criteria for the proposed exemption category under Section __.104(d)(3). As OHRP is well aware from its compliance oversight activities, investigators — who have an obvious conflict of interest — often err in making determinations about whether research meets the criteria for the current exemption categories. Any decision tool could be undermined easily by intentional failure to input complete and accurate information about the proposed research. Therefore, someone other than the investigator who has access to the complete research protocol should make exemption determinations.

(37) In question 48, the NPRM asks: *Public comment is sought on whether this exemption category [described at Section __.104(e)(1)] should be narrowed such that studies with the potential for psychological risk are not included. Are there certain topic areas of sensitive information that should not be covered by this exemption? If so, please provide exemplary language to characterize such topic areas in a manner that would provide clarity for implementing the Rule.*

If the proposed exemption at Section __.104(e)(1) is included in any final rule, it should not apply to any research that involves greater than minimal psychological risk to subjects.

(38) The second proposed exemption category under Section __.104(e) would be:

> (2) Secondary research use of identifiable private information that has been or will be acquired for non-research purposes, if the following criteria are met:
> (i) Prior notice has been given to the individuals to whom the identifiable private information pertains that such information may be used in research; and
> (ii) The identifiable private information is used only for purposes of the specific research for which the investigator or recipient entity requested access to the information.

In question 50, the NPRM asks: *Public comment is sought regarding whether the proposed exemption should be limited to research in which individuals had been informed of the potential future research use of their information, and given the opportunity to opt out of having their identifiable private information used for research. If the proposed exemption should be limited in this way, what information should be included in the opportunity to opt out? If the opportunity to opt out is made a condition of the exemption category how should it be structured (e.g., how long and under what circumstances should it remain in effect) and what, if any, impact should the opt out have on other provisions of the rule, such as the ability of an IRB to waive informed consent for a subsequent research study using the individual's information? Are there other or alternative mechanisms that should be required to respect individuals' autonomy and other interests?*

Yes, the exemption proposed under Section __.104(e)(2) of the NPRM should be limited to research in which individuals have been informed of the potential future research use of their information and given the opportunity to opt out of having their identifiable private information used for research. If an individual opts out, use of that individual's identifiably private information for research should not be allowed for any research under any circumstances as long as the individual is alive.

(39) In question 51, the NPRM asks: *Public comment is sought regarding what should constitute notice for purposes of this exemption category [described at Section __.104(e)(2)]. Given the many different types of data that would be covered by this provision (e.g., data from private entities used for social or behavioral science research, government records for which laws already establish standards for notice, and data publicly available for harvesting from the internet), would it be possible to develop a uniform "notice" requirement? What type of notice, in terms of its dissemination and scope, should be considered to meet this requirement of the proposed exemption? With regard to the dissemination of the notice, should the notice requirement be permitted to be fulfilled through a general public notice, not specifically directed to individuals who are potential research subjects, such as the notice allowable under the Privacy Act? Would a prominent notice posted in all clinics or other relevant public places where information will be collected be acceptable? Should each individual whose data could be used receive their own notice, such as is required of direct treatment providers covered by the HIPAA Privacy Rule? With regard to the content of the notice required by this proposed exemption, what kind of information should be included in the notice, such as the types of research that might be conducted, privacy safeguards, contact information, etc.?*

A uniform, general public notice would not be sufficient or meaningful. Instead, each individual whose identifiable private information could be used should receive his own notice. The notice should include the types of research that might be conducted, privacy safeguards, directions for obtaining more information, and instructions for opting out.

(40) The NPRM proposes to add a new Section __.104(f) stating the following:

> The following categories of exempt human subjects research involve biospecimens or identifiable private information, must be recorded as required in paragraph (c) of this section, require application of standards for information and biospecimen protection as described in Sec. __.105, and require informed consent and limited IRB review to the extent described in each category or otherwise required by law.

The fact that the two categories of research described under proposed Section __.104(f) would require informed consent and IRB review essentially means such research is not exempt. As a result, including these categories under the section on exemptions does not make sense and is likely to cause confusion.

(41) In question 56, the NPRM asks: *Public comment is sought on whether there should be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures (e.g., cheek swab, saliva).*

No, there should not be an additional exemption that would permit the collection of biospecimens through minimally invasive procedures.

(42) In question 57, the NPRM asks: *Public comment is sought on whether research involving prisoners should be permitted to apply any or all of the exemption categories found at proposed Sec. __.104, either if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners, as proposed in the NPRM, or if the research intends to involve prisoners as research subjects.*

We agree with the NPRM's proposal to permit research involving prisoners to qualify for an exemption if the research consists mostly of non-prisoners and only incidentally includes some number of prisoners. We oppose expanding the applicability of any of the exemptions to research involving prisoners when the research is intended to involve prisoners as research subjects.

(43) The NPRM proposes to eliminate the following provision found at Section __.107(b) of the current Common Rule:

> Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

We oppose eliminating this provision from the Common Rule because doing so may result in IRBs having less diverse membership.

(44) The NPRM proposes to add the following new provision at Section __.114(b)(1):

> Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be selected by the Federal

> department or agency supporting or conducting the research or, if there is no funding agency, by the lead institution conducting the research.

We oppose requiring all institutions in the U.S. engaged in any cooperative research study to be required to rely on a single IRB for several reasons. Institutions in the U.S. should be free to voluntarily choose whether to rely on an external IRB for a cooperative research study.

First, this proposal promotes the dangerous misconception that consideration of local context issues are important for IRBs at foreign institutions but not for IRBs at U.S. sites. The position of the NPRM drafters that relevant local contextual issues pertinent to most clinical research can be addressed through mechanisms other than local IRB review for any domestic site but not for foreign sites in multisite studies is dangerously flawed. The drafters appear to be ignorant about the tremendous diversity across the U.S. population in terms of cultural norms, community attitudes, race, ethnicity, spoken language, religion, educational level, and many other factors relevant to judging whether a research project is ethical and satisfies the requirements of the Common Rule. To assert that such local factors are not relevant to considerations made by IRBs for domestic sites in a multisite study but are relevant to considerations made by IRBs for foreign sites is not a defensible position.

Second, such a mandate could impair consideration of valuable local knowledge that enhances protection of human subjects. We note that Section __.107(a) of the current Common Rule requires the following regarding IRB membership:

> The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. … [T]he IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

Furthermore, Sections __.111(a)(3), 111(a)(4), 111(b), and 116 of the current Common Rule require that IRBs ensure the following criteria, among others, are satisfied before approving proposed research:

- Selection of subjects is equitable.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- Informed consent shall be sought in language understandable to the subject and under conditions that minimize the possibility of coercion or undue influence.

These regulatory provisions clearly articulate the importance of an IRB, regardless of location, taking into account local factors when reviewing proposed research. The consideration of these local factors has direct relevance to how well subjects will be protected. Under the NPRM's proposal mandating that all U.S. institutions engaged in a multisite study rely upon one IRB, a single IRB composed of five members could convene a meeting of three members and review and approve a complex multisite clinical trial involving several hundreds of sites across the U.S. with two members voting for approval.

Given the diversity of the U.S. population, it is impossible for a single IRB — even one composed of many more than five members — to have sufficient knowledge of the local research context at all study sites involved in a large multisite study and satisfy the regulatory requirements cited above.

The NPRM's dismissive attitude toward the importance of IRB consideration of the local research context, as reflected in the following statements in the NPRM's preamble, is disturbing:

> This policy would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal IRB reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule. Although a local IRB may conduct its own additional internal review, such a review would not be binding on the local site if not adopted by the single IRB, and the terms of it would not be enforced by OHRP.
>
> Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most studies can be addressed through mechanisms other than local IRB review. For research where local perspectives might be distinctly important (e.g., in relation to certain kinds of vulnerable populations targeted for recruitment), local IRB review could be limited to such consideration(s); but again, IRB review is not the only mechanism for addressing such issues. The evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent form and process generally do not require the unique perspective of a local IRB.

Despite the above assertion, we note that there are no provisions in the NPRM that stipulate mechanisms, other than through IRB review, for addressing relevant local contextual issues. Statements that relevant local contextual issues pertinent to studies can be addressed through mechanisms other than IRB review have no regulatory basis.

Finally, we are concerned that officials at the National Institutes of Health, which has aggressively pursued such a regulatory change and has a conflict of interest in this matter, inappropriately played a key role in crafting this proposed change to the Common Rule.

(45) Proposed Section __.115(a)(3) of the NPRM includes the following:

> … including the rationale for conducting continuing review of research that has progressed to the point that it involves only one or both of the following:
> (i) Data analysis, including analysis of identifiable private information, or
> (ii) Accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition.

This text seems to be redundant with proposed Section __.115(a)(8), which states:

> The rationale for requiring continuing review for research that otherwise would not require continuing review as described in Sec. __.109(f)(1).

One of these provisions should be deleted, or further clarification is needed explaining the distinction between the two.

(46) The NPRM proposes to add the following to the introductory text of Section __.116:

> The prospective subject or the representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. The information must be presented in sufficient detail relating to the specific research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or representative's understanding of the reasons why one might or might not want to participate. In obtaining informed consent, the investigator must present first the information required by this section, before providing other information, if any, to the subject or the representative. Any informed consent form must include only the requirements of informed consent under this section, and appendices that include any other information provided to the subject or the representative. If an authorization required by 45 CFR parts 160 and 164 is combined with a consent form, the authorization elements required by 45 CFR 164.508 must be included in the consent form and not the appendices.

While we generally support the concepts expressed in the first two sentences in the above proposed new text, we are concerned that the subsequent sentences inappropriately conflate *obtaining* informed consent with *documenting* informed consent. If this latter language is retained in any final rule, it should be moved to Section __.117 (Documentation of informed consent).

Furthermore, we are concerned with the statements in the preamble discussing the proposed expansion of the introductory text of Section __.116, which indicate that this new language is intended to lead to "substantially shorter consent forms." Too often, consent forms for research fail to include important details about the purpose of the research, the research procedures, reasonably foreseeable risks and discomforts, and appropriate alternative procedures or courses of treatment that might be advantageous to

the subjects. Encouraging consent forms to be substantially shorter likely will exacerbate these problems.

Investigators have the ultimate responsibility for ensuring that potential subjects fully understand all aspects of the proposed research. Asking subjects to read a consent form, regardless of length, for many research studies would not constitute adequate informed consent. Adequate informed consent, particularly for complex clinical trials, may require hours of discussion between the investigator and the potential subject. The consent form is just one component of a rigorous and meaningful consent process.

(47) Proposed Section __.116(e)(2) of the NPRM states the following:

> (2) Additional criteria for waiver or alteration of consent for biospecimens. For research involving the use of biospecimens, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the above requirements to obtain informed consent, provided the IRB finds and documents the criteria in paragraph (e)(1) of this section, and the following additional criteria:
> (i) There are compelling scientific reasons to conduct the research; and
> (ii) The research could not be conducted with other biospecimens for which informed consent was obtained or could be obtained.

This provision appears to be poorly conceived. First, the first sentence should read (recommended revisions in bold): "Additional criteria for waiver or alteration of consent for **research involving** biospecimens."

Second, it is unclear why the provisions for waiver of informed consent for research involving public benefit and service programs subject to approval of state or local officials under proposed Section __.116(e)(1) are relevant to research involving biospecimens.

(48) Proposed Section __.116(h) of the NPRM states the following:

> (1) A copy of the final version of the informed consent form for each clinical trial conducted or supported by a Federal department or agency must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available federal Web site that will be established as a repository for such informed consent forms. The informed consent form must be posted in such form and manner as the department or agency head may prescribe, which will include at a minimum posting, in addition to the informed consent form, the name of the clinical trial and information about whom to contact for additional details about the clinical trial.
> (2) The informed consent form must be posted on the federal Web site within 60 days after the trial is closed to recruitment.

In general, we strongly support this proposed provision. However, we recommend several changes. First, this provision would be more appropriately placed in Section __.117 (Documentation of informed consent).

Second, this provision should be expanded to apply to (a) all non-excluded, non-exempt research (not just clinical trials); and (b) non-excluded, non-exempt research that is not conducted or supported by any federal department or agency.

Third, posting of the consent forms should not be delayed until up to 60 days after recruitment for a research study is closed. Instead, consent forms should be posted before recruitment begins.

Finally, if documentation for informed consent is waived under Section __.117(c), any written statement regarding the research provided to the subjects in accordance with Section __.117(c)(2) should be posted on a publicly available federal website.

(49) In question 64, the NPRM asks: *Would research subjects continue to be appropriately protected if the definition of "legally authorized representative" were broadened to include individuals authorized by accepted common practice to consent on behalf of another individual to participation in clinical procedures? If the definition of "legally authorized representative" was broadened in this way, public comment is sought on the interpretation of "accepted" and "common" as these terms would be used in the revised definition.*

We oppose expanding the definition of "legally authorized representative" as described in this question.

(50) In question 65, the NPRM asks: *Public comment is sought on how the waiver criterion regarding "practicably" at Sec. __.116(d)(3) could be explicitly defined or otherwise clarified (e.g., what term should replace "practicably"?).*

We favor retaining the term "practicably" and do not see a need for further clarification.

(51) In question 70, the NPRM asks: *Public comment is sought on the proposed prohibition on waiving consent when an individual has been asked to provide broad consent under Sec. __.116(c) and refused. In particular, how would this prohibition on waiving consent affect the secondary research use of identifiable private information? If an individual was asked to provide such consent, should the absence of a signed secondary use consent be considered a refusal? Does this prohibition on waiving consent for the secondary use of identifiable private information create a disincentive for institutions to seek broad secondary use consent and instead seek a waiver of consent from an IRB? Under what circumstances, if any, would it be justified to permit an IRB to waive consent even if an individual declined or refused to consent?*

If an individual has been asked to provide broad consent under Section __.116(c) to storage, maintenance, and secondary research use of biospecimens or identifiable private

information, it would be unethical to waive consent for any future secondary research on that individual's biospecimens or identifiable private information. We therefore support the prohibition against waiving consent under such circumstances and believe it would never be appropriate for an IRB to waive consent even when an individual declined or refused to consent. If an individual was asked to provide broad consent for storage, maintenance, and secondary research use of biospecimens or identifiable private information, the absence of a signed secondary use consent form should be considered a refusal. This prohibition should not create a disincentive for institutions to seek broad secondary use consent and instead seek a waiver of consent from an IRB.

Thank you for the opportunity to comment and for taking our comments into consideration.

Sincerely,

Sarah Sorscher, J.D., M.P.H
Attorney
Public Citizen's Health Research Group

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