Society for Women's Health Research

December 4, 2015

Jerry Menikoff, MD, JD
Office of Human Research Protections (OHRP)
U.S. Department of Health & Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Dr. Menikoff,

The Society for Women's Health Research® (SWHR) is pleased to submit comments to the Office of Human Research Protections (OHRP) regarding the Federal Policy for the Protection of Human Subjects (Docket ID: HHS-OPHS-2015-0008), also known as the Common Rule. SWHR, a national non-profit organization based in Washington, DC, is widely recognized as the thought leader in promoting research on sex differences and is dedicated to improving women's health through advocacy, education, and research.

SWHR was founded in 1990 because women were historically not included in medical research. Although the numbers of women and minority men involved in research has increased since that time, these groups are often still underrepresented in research trials. SWHR supports a proposed update to this regulation and will use this response to provide recommendations to the new ruling based on Common Rule agency questions in the Notice of Proposed Rule Making (NPRM) released in September.

We believe providing a definition of 'biospecimen' will be helpful in implementing this provision and reducing confusion or variability by IRB review committees in implementing the Common Rule. Federal agencies should use this document to clearly delineate what is and is not covered, while leaving room for future innovations.

Of the three proposals for the definition of a human subject, **SWHR supports Alternative A: expanding the definition of a human subject to include whole genome sequencing, as it appears to adequately balance autonomy and beneficence.** In an ideal world,

Alternative B: expanding the definition to only include using technologies that generate unique information, would be best; however, this definition may not be practical or feasible for many research studies.

Alternative A provides protections from easily identifying a person involved in a research study. At the same time, this proposal allows investigators performing smaller, more complex analyses of parts of the DNA to avoid the additional regulatory requirements that would make such studies financially impractical. However, SWHR believes this definition should be revisited every 5-10 years and opened for public comment to respond to rapid changes in science that may require re-defining a "human subject." SWHR has several concerns regarding the initial proposal (to include all biospecimens as human subjects) and Alternative B. In the initial proposal, it may be difficult for institutions to track all biospecimens and would greatly increase IRB scrutiny of reporting requirements. As the updates to the Common Rule are designed to make it easier for IRBs to delineate between ethical and non-ethical research, among other reasons, increasing their workload would not meet such standards.

Alternative B would require investigators to spend more time on an Institutional Review Board (IRB) application, detailing the specific technologies needed or used during their research study. In addition, HHS and other Common Rule agencies will need to create a list of standard technologies that would be included as well as update this list as new technologies are released. Both of these concerns would greatly increase the administrative burden and reduce timeliness of IRB reviews and approvals.

In addition, **SWHR recommends replacing the description "identifiable private information" with "Personally Identifiable Information."** We feel this change should be adequate to reduce confusion and develop consistency with the descriptions used in other areas of the Federal Government. However, its current modifier "may be readily ascertained" should be further defined; particularly the term "readily ascertained." Does this term refer to the amount of time/effort it takes to uncover the private information or does it refer to the ability for someone to obtain the information at all? As stated, the terminology is unclear.

Activities Excluded from Research

SWHR supports the discussion of activities excluded from research (data collection and analysis including the use of biospecimens for an institution's own internal operational monitoring and program improvement purposes) in the preamble. Common Rule agencies should emphasize such exclusions and provide clarification to ensure investigators and institutions comply with the new rules. SWHR also supports the release of guidance for investigators that will further detail these and similar exclusions listed in the Common Rule.

Activities Excluded from Research: Exclusions Due to Educational Tests, Interview Procedures, Observations of Public Behavior

SWHR believes that activities excluding research involving the use of educational tests, survey/interview procedures, and observations of public behavior uninfluenced by investigators would easily remain exclusions, following the outlined conditions. As these activities are intended for assessment and information, they should already be covered by the Privacy Act. Therefore, they should already have sufficient protections under such circumstances.

However, SWHR strongly believes investigators should not be responsible for making self-determinations for these types of activities. Investigators should at least informally consult with their IRB staff member/representative to determine exclusion. Some sort of written documentation, such as an email response, should be generated and retained prior to commencing research.

In addition, requiring notice be given to participants should strike a good balance between autonomy and beneficence. As previously discussed in the NPRM, certain activities may cause stress to participants. Therefore, ensuring that participants adequately understand the overall project and how to opt-out or discontinue is important. The notice does not need to be as extensive as an informed consent process, but a brief description of the research purpose, privacy safeguards, investigator contact information, and information on the ability to opt-out after research has begun should suffice. Excluding these research activities should not produce a reduction or alteration of existing rights or protections. As mentioned in the NPRM, many of these activities occur so often that people participating in such projects usually understand the risks involved. Requiring notice, especially for tests, surveys, and interviews, will help ensure those who are unaware understand any risks involved.

If secondary analysis of data collected under this exclusion is permitted, SWHR believes the statutory, regulatory, and other policy requirements cited in the NPRM will provide enough oversight and protection that expedited review would produce minimal additional subject protections. However, IRBs should be aware of the research study through informal consultation. In addition, the research proposal could be uploaded to an IRB database or registry; similar to ClinicalTrials.gov informing the public of research activities occurring in their community. Research projects conducting secondary analysis of such data should still be subject to the same security and privacy conditions. Additionally, participants should have been notified prior to the initial study that their responses may be subject to secondary use and analysis.

Activities Excluded from Research: Research Involving the Collection of Publicly-Available or Completely De-Identified Data

Since data in this exclusion category are publicly available or completely de-identified, SWHR believes Common Rule agencies should be able to rely on investigators to make self-determinations for these types of research activities. However, the relevant IRB should be

notified of their research project and documentation should be generated and retained in the event of any future questions or concerns.

To assist in making such determinations, Common Rule agencies should define what comprises "publicly available" data in a narrowed version of this exclusion. For example "publicly available" may be defined as a Google search, a shared database with investigator-only access, data that was private but exceeded some set term limit (e.g., after participant death or 50 years after collection), or any combination of the above. Federal agencies need to clarify what is "publicly available" to ensure investigators and IRBs are able to determine if an exclusion applies.

Activities Excluded from Research: Research Conducted by the Federal Government Using Government-Generated or –Collected Information Obtained for Non-Research Purposes

SWHR believes investigators within the federal government using government generated data should be able to self-determine if their research activity is covered under this exclusion. However, any self-determination should be made in consultation with agency/bureau leadership and/or IRB staff or representative. Documentation of their encounters and final decision should be generated and retained. Documentation could be retained in an internal or external registry/database, similar to ClinicalTrials.gov.

In addition, a separate exclusion should be developed to address research involving similar information collected by non-federal entities, even if comparable privacy safeguards are in place. Given state laws and regulations differ, Common Rule agencies should specifically address "comparable" or standard privacy safeguards that should apply.

Activities Exempted from Research

Common Rule agencies could improve language in the regulations by providing more specific examples of research studies that qualify (or do not qualify) for these exemptions. Developing guidance for investigators and IRBs, in consultation with all Common Rule agencies, will greatly assist in making these types of determinations in the future.

Activities Exempted from Research: Exemption Determination Tool

SWHR cautiously supports the development of a federal exemption determination decision tool; recommending federal or IRB oversight and auditing of responses. If such a tool is created, results should be retained by investigators, posted on a research information website, and shared with a sponsoring institution or IRB to maintain public trust in research. Transparency is key to ensuring that ethics violations do not occur.

In addition to the study abstract, privacy safeguards, and notice/consent documents used, investigators should retain contact information and biographies of primary investigators and their recruitment strategies for human subjects to submit to the exemption determination tool.

SWHR believes it is highly unlikely that any determination tool could be developed that will prevent investigators from submitting false or contrived responses 100% of the time. In fact, investigators could do so now by misleading IRB reviewers in their application. Common Rule agencies will have to trust the ethics of the investigators in this case. One way to reduce the likelihood of such occurrences would include periodic auditing of the decision tool by federal agencies. In this case, agencies would review decision tool records and follow-up with a select group of investigators to discover if their research is proceeding as submitted in the tool. Another option could include a requirement for investigators to submit their decision tool results to an IRB prior to starting their research. While the exemption decision could not be changed, it would allow other institutions to hold investigators accountable for their research.

SWHR recommends the concurrent development of an in-person or all-day training on research activities qualifying for exemption and appropriate use of the determination tool to reduce misuse. This should not be limited to an online-only training with minimal testing/feedback requirements as current OHRP and other human subject protections trainings have consisted of to date. Instead, training should focus on in-depth skills for developing and submitting ethical research designs for exemption determination. Common Rule agencies should offer in-person training every 2-3 years for IRB staff and principal investigators, with additional training opportunities available online via webcast. Finally, SWHR recommends requiring all new investigators to undergo full IRB review for their first research project, whether or not it qualifies for exemption/exclusion. This requirement will allow the new investigator to understand the process and assist with developing appropriate proposals in the future.

Activities Exempted from Research: Exemptions for Research Involving Benign Interventions & Low-Risk Studies

Requiring notice will strike a good balance between autonomy and beneficence for this type of research. However, the notice does not have to be as extensive as an informed consent and should be able to be given "on the spot" or right before such recording or surveys take place either orally or in writing.

In addition to the research purpose, privacy safeguards, and contact information for investigators; notices should include any risks from research, an explanation of what participants might be doing or will undertake, and information to opt-out of the study. Prospective subjects should always be given the explicit opportunity to opt-out prior to participating in the study as well as informed if they can opt-out after it has started.

SWHR recommends this exemption category be narrowed for psychological risk, as these studies may cause lasting mental health effects on subjects. Topic areas that should not be covered under such exemptions include trauma or PTSD-related studies, domestic and dating violence, and child abuse.

Activities Exempted from Research: Secondary Use of Identifiable Private Information Acquired Initially for Non-Research Purposes

SWHR believes it is necessary to develop a uniform notice requirement for this exemption category, inclusive of clinical registries, as the nature of such systems are to promote disease-specific research. This uniform notice could be given at the start of any non-research activity under this exemption alongside informed consent, as some opportunities may arise to conduct activities in a population at the same time they learn about the opportunity.

The notice requirement could be fulfilled through a general public notice, however each individual whose data could be used, including those who were participants in previous studies, should receive their own personal notice. Investigators have a responsibility to ensure their participants understand that they own their information. As a result, the exemption should include the notice requirement in order to exempt such studies from IRB review. Examples of information that should be listed in a brief notice include types of research to be conducted, privacy safeguards, and investigator contact information.

This exemption should be limited to research involving information from individuals who were informed of the possibility of future research use of their personally identifiable information and given an opportunity to opt-out. Research institutions should implement a blanket notice to all patients that research may be conducted with their information in the future. The notice should include contact information to notify a designated institution representative if they would like to opt-out. This opportunity to opt-out of future research should be fairly simple; in line with proposed changes to informed consent.

To maximize autonomy, an individual's request should remain in effect permanently until/unless the individual contacts the data collector/researcher (directly or as a participant in another non-research project) and indicates they can use their information moving forward.

Informed Consent

Common Rule agencies should address several major topics in a future guidance to investigators and lawyers on informed consent:

1) *Literacy*: Guidance should discuss the importance of "readability" of the informed consent, such as the literacy levels of proposed participants. Informed consent (as well as appendices and legal/institutional requirements) should be written at a level that accounts for the average literacy level of the population being studied. In addition, health and science literacy is often far lower than the reading literacy of a population; thus requiring even simpler terms to describe procedures in health-related research.
2) *Cultural Competency*: When developing informed consent documents, investigators and lawyers should understand the effects that culture, including gender and environment, play on the "understandability of informed consent." For example, women may read and process a document differently than men or feel more/less likely to ask questions regarding areas they do not understand. In addition, language or cultural barriers may hinder correct

interpretation of the information listed. Testing the informed consent document with a small group of potential participants, e.g., women, men, individual racial/ethnic groups, may help eliminate this issue.

3) *Length*: SWHR supports Common Rule agencies' assertion that informed consent documents should be brief. Agencies should develop further guidance on what constitutes "brief," possibly setting page/attachment limits.
4) *"Essential Items:"* SWHR believes that Common Rule agencies should develop guidance clearly defining which items are specifically considered "essential" and should be listed on the informed consent.

Informed Consent: Strengthening Informed Consent through Broadening "Legally Authorized Representatives"

SWHR believes that the definition of "legally authorized representative" should not be broadened to include individuals that consent on behalf of clinical procedures. Given research studies often include experimental procedures, a stricter definition is warranted. For example, home health staff are often authorized to give consent for participation in clinical procedures for individuals unable to do so for themselves; however, they may not have the best interests of the individual in mind if allowing them to participate in research studies.

Informed Consent: IRB Waivers of Consent

The prohibition on waiving consent after individual refusal for secondary research use will limit use of certain data and investigators may have to redesign their experiments or adjust their population. However, that prohibition is not necessarily considered detrimental to the research process.

The absence of a signed secondary use consent **MUST** be considered a refusal. As the investigator does not know if the individual would consent to such use of their information, they should not assume it is "Yes." In this case, it could be permissible for an investigator to contact the individual to obtain consent prior to proceeding with their research study. There should be **NO** circumstances for an IRB to waive consent if an individual declines or refuses consent. It is incredibly important to respect the right of the individual to maintain their own information.

In addition, the term "practicably", as defined by the NPRM (feasible, capable of being effected/put into practice, capable of being done/accomplished) is sufficient to describe research requirements for waivers of consent. Federal agencies should follow up with guidance for IRBs and/or investigators providing examples of what may be approved or not to further clarify this issue.

Privacy Safeguards

Specific information security measures should be required for certain types of information or research activities and such safeguards should be calibrated to sensitivity. As a result, having HHS publish a list separated by sensitivity/risk categories would be most helpful and provide more flexibility to investigators and institutions.

Privacy Safeguards: Research Activities Regulated by the HIPAA Privacy Rule
Research activities regulated by the HIPAA Privacy Rule should not be excluded from IRB oversight and review. Often, even HIPAA-covered facilities find these rules confusing regarding what they can and cannot do to protect individual privacy. Therefore, the HIPAA rules are not sufficient at this time and continuing to seek IRB approval will add meaningful protection to human subjects. As such, these research activities should be subject to the Common Rule at least until HIPAA can be better clarified, promulgated, and updated to be equal to or more stringent than the Common Rule.

Privacy Safeguards: Notification of Clinically-Meaningful Research Results
As stated in the NPRM, the advent of more sophisticated technologies and greater accessibility of large datasets will pose difficulties in ensuring that an individual could never be identified from a biospecimen. The secondary use of biospecimens, particularly for whole genome sequencing purposes, could produce specific moral disruptions for informed consent as well as confidentiality. Regarding informed consent, the shared aspects of the genome raise the question about the reach of informed consent moving beyond the individual to biological relatives. Any information that is gathered from biospecimens used for whole genome sequencing purposes is not limited to the individual who gave informed consent for the original research study. As informed consent and confidentiality are intimately related, confidentiality should also be considered.

There have been cases where courts have found that physicians had a duty to warn family members about genetic diagnoses that might have helped those individuals make important decisions regarding their health.[i] In such cases, breaching confidentiality was seen as necessary for practitioners to fulfill the moral obligation of beneficence. While the obligations of physicians are quite different than those of investigators, the Common Rule NPRM mentions that "in a significant percentage of instances investigators will be learning information, not necessarily related to the specific purpose of their studies that would nonetheless be significant to participants in terms of making decisions about their health care." (p. 156) As the potential outcome of disclosing or not disclosing information to participants is the same whether the information is held by a physician or investigator, it is not unwarranted to consider the similarities between the moral obligations of the two types of professionals.

Mandating Single IRB Review for Cooperative Research
SWHR is supportive of a single IRB review, yet is concerned this is not a realistic option at this time. This option should benefit institutions by reducing time for IRB review while resolving any conflicts that may arise if one IRB approves a project proposal and another does not. However, if multiple institutions are working together on a research study, they may have difficulty choosing the primary IRB or still require the review of their institutional IRB prior to commencing the research project at their location. Simultaneously, local IRBs should still retain some measure of authority to protect their populations.

If implemented, Common Rule agencies should develop language to assist investigators when these and other potential conflicts arise. Examples include developing a regulation stating the institution where a certain percentage of research or participants are housed will designate the primary IRB; developing a set of model written agreements for institutions on cooperative research and single IRB review; or developing OHRP-led trainings for institutional investigators, human research protections departments, and legal teams on how to implement this rule effectively.

The Common Rule should include limited criteria for federal agencies or departments seeking exemptions to the single IRB review regulation. Federal agencies should have the flexibility to apply agency-developed criteria based on their own departmental needs, regulations, and research portfolio. However, a standardized set of overarching rules will assist IRBs with managing interactions between different departments moving forward.

Expedited Review for Studies Qualifying as "Minimal Risk"

SWHR believes a list of "minimal risk" activities developed by the HHS Secretary will be a useful tool for the research community. The list will provide guidance to investigators and IRBs, while permitting IRB jurisdiction in determining if a proposal should be referred to full review. Creating this list should help standardize expedited review activity qualifications.

SWHR supports the eight years proposed for updates to the Secretary's list of minimal risk activities. However, SWHR recommends that HHS should align these updates with other updates to Common Rule-related products so all changes are released at the same time, making it easier for institutions to implement.

Finally, advice should always be solicited from outside parties when updating the list. Investigators and IRB reviewers are best positioned to provide insight on some areas that may be on the list yet have had to repeatedly re-classify for full review, as well as other areas that should be included on the list yet were not included in the most recent update.

Research Conducted in Vulnerable Populations

SWHR believes the Common Rule focus on coercion and undue influence will follow the definition of vulnerability. Separately identifying individual groups has led to unnecessary stigmatization and reductions in opportunities for research in the past. For example, limited animal studies of drug interactions in pregnancy are often all the information medical professionals have prior to prescribing an FDA approved drug for pregnant women, as investigators often do not conduct research in this population due to widely published, unethical studies conducted in the past. Increased opportunities for pregnant and lactating women in Phase III clinical trials or other research will help improve knowledge, but only if investigators understand how to appropriately incorporate pregnant women and other traditionally vulnerable groups into research study designs.

As a result, SWHR believes the Common Rule needs to emphasize the importance for IRBs to spend significant time considering whether the study involves a vulnerable population, while providing them the flexibility to deem a population "vulnerable" based on the ethics of the individual study; not on a federal list.

However, Common Rule agencies must reference the history of clinical trials and research studies exploiting different populations as examples without setting specific categories in future guidance related to ethical research conduct. Such guidance must address well-documented exploitations such as Nazi human experiments and Tuskegee Syphilis Study, as well as more recent studies.

For example, the guidance could reference the 2004 suicide of Dan Markingson after enrollment in a University of Minnesota/AstraZeneca clinical trial for Seroquel. In this case, he was enrolled under threats of involuntary commitment to a psychiatric facility.[ii] The guidance could also reference a 1991 study sponsored by the U.S. Centers for Disease Control and Prevention (CDC) and Kaiser Permanente which failed to inform parents they were using an experimental, unlicensed vaccine to study its effects on protecting children during a measles epidemic in Los Angeles.[iii] Finally, the guidance could also address the 2004-2005 Children's Environmental Exposure Research Study (CHEERS) sponsored by the U.S. Environmental Protection Agency (EPA), among other funders, which inadequately provided informed consent and offered an incredibly high incentive, later recognized as coercive, for low-income populations to participate.[iv]

The guidance should discuss these cases and address lessons that investigators must learn from these recent research studies, such as informing participants of all risks (including uncertainties) associated with the research and consulting with community members from the population of potential participants to receive feedback on study materials and design.[iv] The guidance should also address oversight strategies that principle investigators can use to ensure equitable recruitment across all research sites.

Finally, guidance should include recommendations and outreach strategies for investigators to follow-up with participants regarding the results of the research study. Often, investigators only involve participants during the study and do not follow-up regarding overall results; which can also be perceived as exploitation. As a result, involving participants after research results are analyzed, even brief updates, will help reduce barriers to participation in future studies.

Clinical Trials

Common Rule agencies should include a policy that extends Common Rule oversight to all institutions currently receiving federal support, at any monetary threshold value, at the time of the clinical trial application. Many institutions receiving federal funding in the past are likely to continue seeking it; limiting the concerns for setting a specific timeframe or minimum value. Setting a federal policy also reduces the burden in tracking the federal financial support status of the institution.

As this rule is finalized, SWHR recommends additional descriptive information on how Common Rule agencies plan to harmonize on guidance moving forward. Greater harmonization is important but should be appropriately balanced with developing guidance that is approved and released in a timely manner.

Agencies should clarify how they plan to do this, such as bringing other agencies in during the guidance planning and development phases prior to going through the full approval process. Also, agencies should clarify whether all cooperating agencies must formally approve guidance to support harmonization. If so, the publication process may be delayed as it goes through multiple approval processes. Developing a streamlined, inter-departmental approval process for these types of guidance may be necessary moving forward.

Thank you for the opportunity to comment on the NPRM, we look forward to reviewing the final regulation when it becomes available. If you have any questions, please contact Andrea Lowe at Andrea@swhr.org.

Sincerely,

Phyllis Greenberger, MSW
President and CEO
Society for Women's Health Research

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[i] https://h2o.law.harvard.edu/collages/8876
[ii] http://www.motherjones.com/environment/2010/09/dan-markingson-drug-trial-astrazeneca; https://www.documentcloud.org/documents/1690025-markingson.html
[iii] http://articles.latimes.com/1996-06-17/news/mn-15871_1_measles-vaccine
[iv] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1805023/