National Congress of American Indians

Comments on

Advanced Notice of Proposed Rulemaking (ANPRM) for "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators"

October 25, 2011

The National Congress of American Indians (NCAI) appreciates the opportunity to provide comments and other information to the U.S. Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) on the proposed rulemaking (ANPRM) regarding how current regulations for protecting human subjects who participate in research might be modernized and revised to be more effective. NCAI seeks to better protect American Indian and Alaska Native tribes and peoples who participate in research.

NCAI is the oldest and largest national organization representing the interests of American Indian and Alaska Native tribal governments in the United States. It is a membership organization that serves the interests of the 565 federally-recognized tribes, state-recognized tribes, and American Indian and Alaska Native citizens. In 2003, NCAI established the National Congress of American Indians Policy Research Center (NCAI PRC) to serve as a tribally-driven center, focusing solely on issues facing tribal communities. The NCAI PRC provides the resources and tools necessary to inform public policy debates with meaningful information and assist in shifting the discourse in Native policy from a problem-focused approach to truly proactive, future-thinking strategy development. The NCAI PRC's tribal research regulation work serves to support tribal leaders in ensuring research that is conducted on their lands and with their citizens is ethical, affirms tribal sovereignty, and contributes to community well-being.

There has been a long and challenging history of research in American Indian and Alaska Native communities. American Indian and Alaska Native people are one of the most heavily-studied groups in the United States. Unfortunately, the long history of research in Indian Country has included some instances of harm to American Indian and Alaska Native tribes and peoples. Many Native peoples are wary of research and do not trust researchers. This is largely due to the fact that the term "research" generally reminds Native peoples of the myriad projects historically conducted that did not benefit Native communities, and even, in some cases, resulted in harm to these communities.

The most recent, public example of harmful research in Indian Country is described in the now-infamous lawsuit the Havasupai Tribe filed against the Arizona Board of Regents. In February 2004, the Tribe filed the lawsuit, charging that researchers from Arizona State University (ASU) misused blood samples taken from tribal members. The Tribe claimed that tribal members were told their blood samples would be used for a study on the genetics of diabetes. However, the samples were also used for studies on schizophrenia, inbreeding, and possible migration patterns of the tribe's ancestors from Asia to America. The case was recently settled out of court. This case sent waves throughout Indian Country and the research world, with many tribes and American Indian and Alaska Native organizations, including NCAI, passing resolutions

expressing support for the Havasupai Tribe's lawsuit against the Arizona Board of Regents. This case also caused many American Indian and Alaska Native communities to seek new ways to protect themselves from being deceived about the purposes of research projects and to control how their communities are portrayed in publications or presentations by researchers.

NCAI recognizes the critical need for meaningful and clear Institutional Review Board (IRB) regulations to protect human subjects. Yet, NCAI has concerns that these proposed changes would have major implications for research conducted with American Indian and Alaska Native tribes and peoples. As such, in our comments below, NCAI advocates that the sovereignty of tribal governments, as nations, be acknowledged in all aspects of research regulation and IRB rules. Specifically, NCAI submits comments that call for:

- Initial and continuing review of research with American Indian and Alaska Native tribes and peoples by IRBs;
- Continued oversight of and protection over informed consent processes in all research involving American Indian and Alaska Native tribes and peoples;
- Specific oversight in instances where informed consent processes must consider both individual and tribal consent;
- Oversight of any proposed secondary uses or analyses of data collected;
- Acknowledgement of the complexities around de-identification of data due to the small size of communities and unique characteristics of American Indian and Alaska Native tribes and peoples in the larger population;
- The inclusion of tribal IRBs and other research review processes in the revised regulations; and
- Coordination across tribal, community-based, regional, institutional, and national research review bodies to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty.

NCAI urges DHHS to be conscious of the challenging and complex history that American Indians and Alaska Natives have faced and continue to face with regards to research, as well as to be mindful of the opportunity DHHS has to foster a meaningful research ethic going forward so that research can have a positive impact in American Indian and Alaska Native contexts. NCAI advocates that all research conducted with American Indian and Alaska Native tribes and peoples should be developed in full consultation and in equal partnership with tribal leaders over the course of the entire research process, including: research design, data collection, data analysis, and reporting and dissemination. Tribal leaders have the best sense of what kinds of research and data would be most helpful to their citizens. Furthermore, given the diversity and uniqueness of American Indian and Alaska Native communities, the potential risks, benefits, and considerations related to participating in a research study will vary by tribe and by research study. For this reason, American Indian and Alaska Native individuals and tribes must have the opportunity to consent to participate in research in an informed and ethical way.

American Indian and Alaska Native tribal nations are recognized sovereign nations with the authority to regulate all affairs on their lands, including research. A tribe's sovereignty is critical to consider as part of examining IRBs and research regulation policy in Indian Country. The

Obama Administration has specifically committed to direct government-to-government dialogue with tribal nations through the President's 2009 Executive Memorandum directing all federal agencies to comply with Executive Order 13175. This type of direct consultation is necessary for major proposed policy changes, such as those related to human subjects protections in research. NCAI recommends formal tribal consultation by DHHS regarding the proposed changes to IRB regulations so that tribes can directly express their views to OHRP.

NCAI offers the following comments and responses to the DHHS's questions on proposed changes to the IRB regulations to help inform the process that is being conducted. Our responses below are grouped by theme, with references to the relevant questions from the ANPRM. These themes are noted in boldface and emerge from the NCAI Policy Research Center's work related to tribal research regulation. These comments reflect NCAI's best experience and insight to date given our work in the tribal research regulation domain, but we also acknowledge that we continue to consult with tribal leaders and researchers to shape ongoing best practice toward protecting American Indian and Alaska Native tribes and peoples and encouraging meaningful research.

A. Continuing and close review on a consistent and regular schedule by Institutional Review Boards (IRBs) should be required for studies conducted with American Indian and Alaska Native tribal nations and communities.

Question 2: Would the proposals regarding continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?

NCAI recommends that studies conducted with American Indian and Alaska Native tribes and peoples require some form of continuing review. The timeframe should be agreed upon by the American Indian and Alaska Native tribal nation or community at the beginning of the project development. NCAI recommends this review happen at least every two years and in the project's final year. In the Havasupai Tribe's case mentioned above, the university IRB did not review the study after the first approval. Secondary data analyses were conducted that were not authorized by the original consent process. Ongoing review by the IRB might have identified the unapproved secondary use of the data and residual harm to the tribe.

IRBs should consider continuing review for studies that qualified for expedited initial review in cases where research is being conducted where issues related to individual and tribal consent are involved, where anonymity and confidentiality have been guaranteed to research participants and/or tribes, or where any secondary analyses of data are being proposed.

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

NCAI recommends that all studies conducted with American Indian and Alaska Native tribal nations and communities that pose greater than minimal risk should be required to have continuing review annually regardless of whether the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt status. As stated in our response to Question 2, we believe that continuing review of research studies will ensure that secondary analyses are not being conducted without consent and that the rights of American Indian and Alaska Native tribes and peoples are being protected throughout the research process.

Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR 46.111 should not apply to a study that qualifies for expedited review?

NCAI recommends that all of the criteria for IRB approval under 45 CFR 46.111 should apply to expedited studies. NCAI advocates that regulations should not be "relaxed" in the revised proposed rules. Protection of human research participants should still be robust and clearly defined given history of cases with harms in research studies in American Indian and Alaska Native and other communities whose rights have been disregarded by researchers and who have been negatively impacted by insufficient human subject protection within the realm of research review and regulation.

Question 11: What are the advantages of requiring that expedited review be conducted by an IRB member? Would it be appropriate to instead allow such review to be done by an appropriately trained individual, such as the manager of the IRB office, who need not be a member of the IRB? If not, what are the disadvantages of relying on a non-IRB member to conduct expedited review? If so, what would qualify as being appropriately trained"? Would the effort to make sure that such persons are appropriately trained outweigh the benefits from making this change?

NCAI recommends that expedited review be conducted by an IRB member and not a trained staff member in an IRB office. Official IRB members are tasked with the ethical responsibility to uphold their duties and responsibilities in their role for the protection of human subject and the ethics and integrity of the science. A staff member may not have the same duty of care that is necessary to protect the rights of American Indian and Alaska Native tribes and peoples as part of a human subjects protocol.

B. Institutional Review Boards (IRBs) should make the decision about whether a study is "exempt" or "excused;" researchers should not be allowed to just register their studies and then proceed with the study without IRB approval.

Question 19: Regarding the Excused category, should there be a brief waiting period (e.g. one week) before a researcher may commence research after submitting the one-page registration form, to allow institutions to look at the forms and determine if some studies should not be Excused?

NCAI recommends that the IRB should determine whether a research study is exempt or excused rather than allowing researchers to register their studies involving American Indian and Alaska Native tribes and peoples as "exempt" or "excused". Periodic audits do not substitute for initial IRB review prior to when a study commences. NCAI recommends a waiting period longer than

one week before a researcher may commence research after submitting the one-page registration form. This waiting period should be the full time period that the IRB needs to actually review the application and not just the one-page registration form. Essentially, the IRB should still be required to review applications for "excused" research – even if only one IRB member reviews it. Reviewing the entire application will allow a research project to begin only if approved and not cause a situation where damage could be done to the study participants with no recourse. When harm has already occurred (e.g., the Havasupai case), rectifying the problem is much harder than preventing it in the first place.

Question 21: Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category? Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements? Should some other method besides a random selection be used to determine which Excused studies would be audited?

NCAI does not recommend retrospective audits of research projects when this process serves to replace initial review of research studies. A retrospective audit cannot reverse harm or adequately protect research participants. Rather, there should be an IRB review of all studies involving American Indian and Alaska Native tribes and peoples.

Question 22: Are retrospective audit mechanisms sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin a study? Might this new audit mechanism end up producing a greater burden than the current system? Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category? By allowing researchers to make their own determinations, without prospective independent review, will protections for some subjects be inappropriately weakened? If allowing researchers to make such determinations without independent review would generally be acceptable, are there nonetheless specific categories of studies included in the proposed expansion for which this change would inappropriately weaken protections for subjects? And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?

NCAI believes that retrospective audit mechanisms are not sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin the study. This new proposed audit mechanism will create a greater burden on research subjects and communities that are the focus of the research when studies are found to violate human subjects ethics protocols. Retrospective audits do not adequately protect research participants. A one-page registration form will not give sufficient information to enable to them to conduct audits. A brief paragraph abstract may not highlight all methods of research to allow the institutions to make an informed decision on the ramifications of the research study.

C. Secondary use of data or specimens holds potential for harm to individuals and communities.

Question 14: Are these expansions in the types of studies that would qualify for this Excused category appropriate? Would these changes be likely to discourage individuals from

participating in research? Might these changes result in inappropriately reduced protections for research subjects, or diminished attention to the principles of respect for persons, beneficence, and justice?

NCAI does not recommend expansions in the "Excused" category as they are not appropriate. NCAI does not feel that secondary analysis (i.e., use of "preexisting specimens or data") should be allowed without IRB approval for specific secondary studies. Our reasoning is that potential for harm exists if research is conducted without IRB review and/or American Indian and Alaska Native tribal nation authorization of secondary studies (e.g. Havasupai case).

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) above? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?

NCAI recommends that waiving consent should not be permissible under any circumstances for research involving collection and study of existing data and biospecimens. It does not matter if existing data and specimens were collected originally for research or other purposes. All secondary use of data and specimens should require informed consent by research participants. Again, *Havasupai Tribe v. Arizona Board of Regents* is a perfect example of an instance of unauthorized secondary use that can clearly result in harm of research participants when the full intention of a study is not disclosed. Under current tribal laws, there are some instances in which consent for secondary use is required from both the tribal nation and individuals due to the sovereign status of American Indian and Alaska Native tribal nations, as they have the jurisdiction to regulate research including specimen and data use.

Question 45: Under what circumstances should future research use of data initially collected for non-research purposes require informed consent? Should consent requirements vary based on the likelihood of indentifying a research subject? Are there other circumstances in which it should not be necessary to obtain additional consent for the research use of currently available data that were collected for a purpose other than the currently proposed research?

NCAI recommends that future research use of data initially collected for non-research purposes require informed consent for secondary analysis or research conducted on data and specimens. NCAI is concerned about the precedent of secondary use due to the potential for harm on research participants, such as in the *Havasupai Tribe v. Arizona Board of Regents* case, where participants were not made aware of, let alone asked to consent to, the secondary use of specimens collected from them for another study. Regardless of whether the secondary data could be identifiable or not, some American Indian and Alaska Native peoples believe that human tissue, blood, and other biological specimens are sacred as they contain a person's essence and spirit. For this reason, sharing specimens between investigators or moving them from facility-to-facility is worrisome and spiritually concerning for tribal nations and peoples. Other potential harm may occur when tribal nations' names are linked to biological specimens, genetic material, or other kinds of data. Even when a sample or data point does not identify the individual participant, the tribal nation may be named. If specimens and data are then used for secondary analysis in ways not authorized by the tribe, there is the potential for group harm and stigmatization of the tribe in resulting publications and reports.

NCAI acknowledges the Alaska Area Specimen Bank as a potential model of tribal oversight of research that ensures ethical and informed collection and management of biological specimens in a way that provides crucial data to researchers. The Alaska Area Specimen Bank includes biological specimens donated by nearly 92,000 people, most of whom are Alaska Native. The Arctic Investigations Program of the Centers for Disease Control (CDC) in Anchorage, Alaska, houses the specimen bank. The biological specimens in the bank have been collected from Alaska Native people who have participated in research studies, public health investigations, and clinical testing over the last half century. Oversight of the Specimen Bank is now provided by the Alaska Area Specimen Bank Working Group, which includes representatives from the CDC and Alaska Native tribal and community organizations. This Working Group is responsible for the development of policies and procedures governing the collection, storage, and reuse of specimens. Researchers wishing to use specimens contained in the bank must obtain permission to use stored specimens from the Tribal Health Organization of the area where the study participant's specimens were collected and the Alaska Area IRB. Research study proposals must have tribal approval before any research activities are allowed to begin.

Question 46: Under what circumstances should unanticipated future analysis of data that were collected for a different research purpose be permitted without consent? Should consent requirements vary based on the likelihood of indentifying a research subject?

NCAI recommends that any future use of data that were collected whether anticipated or not require consent for secondary analysis or research conducted on data and specimens for the reasons stated above under question 45. Unanticipated harm to individuals or tribal communities may result from secondary use of biological specimens and other data. Therefore, informed consent should be required for any proposed secondary use of data. Even if an individual is not identifiable in the data, a tribe may be. As sovereign nations, tribes have jurisdiction over research conducted using information collected on their land and from their citizens; and, as such, their rights must be considered as part of the informed consent, data reporting, and data ownership processes.

Question 47: Should there be a change to the current practice of allowing research on biospecimens that have been collected outside of a research study (i.e. "left-over" tissue following surgery) without consent, as long as the subject's identity is never disclosed to the investigator?

NCAI recommends that the regulations be clarified regarding the current practice of allowing research on biospecimens that have been collected outside the research study to require consent, regardless of whether a research participant's identity is never disclosed to the investigator. NCAI is concerned with the secondary use of these specimens without informed consent due to potential for harm of the individual participants and tribal communities as groups. Biospecimens that are collected outside of the research study such as "left-over" tissue and blood may be considered sacred by tribal nations and peoples and so sharing them between investigators or moving them from facility-to-facility may circumvent the human subject protection provided as part of informed consent processes.

Question 48: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biopspecimens?

NCAI asserts that there is no circumstance in which it would be appropriate to waive the requirement to obtain consent for additional analyses of biospecimens for the reasons stated above.

Question 52: Should the new consent rules be applied only prospectively, that is, should previously existing biospecimens and data sets be "grandfathered" under the prior regulatory requirements? If so, what are the operational issues with doing so?

NCAI believes there are several operational issues with regulating research projects under two sets of regulations. In an effort to allow for the fullest clarity and least ambiguity, NCAI recommends that regulations related to previously existing biospecimens and data sets require consent for any secondary use.

Question 53: In cases in which consent for future research use is not obtained at the time of collection, should there be a presumption that obtaining consent for the secondary analysis of existing biospecimens or identifiable data would be deemed impracticable, such that consent could be waived, when more than a specified threshold number of individuals are involved? (SACHRP provided the Secretary with recommendations on this issue.) If so, what threshold number should constitute impracticability? Is the number of potential human subjects the only measure of impracticability?

NCAI recommends that no presumption should be made that obtaining consent for analysis of existing specimens is impractical; secondary use of specimens should not be allowed without informed consent from research participants. Secondary use of data without proper informed consent of research participants holds potential for harm as in the *Havasupai Tribe v. Arizona Board of Regents* case.

Question 62: If investigators are subject to data security and information protection requirements modeled on the HIPAA Rules, is it then acceptable for HIPAA covered entities to disclose limited data sets to investigators for research purposes without obtaining data use agreements?

NCAI recommends that limited data sets should not be shared outside the original research team without permission from individual research participants and tribal nations involved in the study. This kind of sharing of data without tribal authorization was part of the problem in the *Havasupai Tribe v. Arizona Board of Regents* case. The sharing of data outside the original research team falls under NCAI's broader concern about secondary use of specimens. There are models for making data accessible to outside research teams without compromising tribal confidentiality, such as a data enclave – or a secure space for researchers to perform analyses that require a protected or controlled environment. The National Institutes of Health has offered data enclaves as an option for the original research team to retain control over data, but to provide the aggregate results of secondary analyses to outside requesting research teams in an ethical way.

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-indentifying such data a sufficient protection, or should there in some instances be requirements preventing the researcher from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?

NCAI recommends that IRBs work to ensure that researchers abide by data sharing, use, review, and dissemination agreements stated in research review applications; and that IRBs pay particular attention to the complexities around de-identification of data due to the small size of tribal communities and unique characteristics of tribal nations and peoples in the larger population that may require initial and continued research review.

D. Potential harms to certain groups should be considered by IRBs, not just the risks to individual participants.

Question 4: Should the regulations be changed to indicate that IRBs should only consider "reasonably foreseeable risks or discomforts"?

NCAI recommends that IRBs should consider potential group harms to historically marginalized populations and other vulnerable groups, including American Indian and Alaska Native tribal nations and communities. Group stigmatization and harm is a very real risk of research conducted in Indian Country as is shown in the past case of Barrow Alcohol Study.[i] In this case, researchers stigmatized the community by stating that the tribe was "practically committing suicide" due to alcohol abuse, and there were resulting painful implications for the community. IRBs should be directed by federal regulations to consider group risks when dealing with American Indian and Alaska Native tribal nations and communities and other similarly distinct groups and communities.

Question 27: The Common Rule currently states (45 CFR 46.111(a)(2)) that an IRB "should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among the research risks that fall within the purview of its responsibility." Do IRBs correctly interpret this provision as meaning that while they should be evaluating risks to the individual subjects participating in the a study, it is not part of their mandate to evaluate policy issues such as how groups of persons or institutions, for example, might object to conducting a study because the possible results of the study might be disagreeable to them? If that is not how the provision is typically interpreted, is there a need to clarify its meaning?

NCAI recommends that IRBs should consider potential group harm to historically marginalized populations and other vulnerable groups, including American Indians and Alaska Native communities. Group stigmatization and harm is a very real risk of research conducted in Indian Country as discussed above.

E. Tribal research review is important because tribal IRBs and other research review boards have unique knowledge about tribal and local contexts that should be respected.

Question 6: Are there survey instruments or specific types of questions that should be classified as greater than minimal risk? How should the characteristics of the study population (e.g. mental health patients) be taken into consideration in the risk assessment?

The same survey instrument or types of questions might be considered minimal risk in one population, but greater than minimal risk with another group. For example, questions about topics that have been historically sensitive in American Indian and Alaska Native communities, such as alcohol use or genetic risk, may be considered higher risk than if the same questions

were asked of other groups. Individual studies should be assessed by local IRBs or review boards to determine what level of risk is posed to potential study participants. Notably, tribal nations have a variety of research review structures. Some tribal nations have their own formal IRBs, while others have developed alternative forms of research review committees or processes. The local research review process a tribe has developed, regardless of its form, can help to ensure risks specific to the population will be minimized. Tribal IRBs and other review boards may have more insight about potential participants' ways of life, cultures, languages and community traditions that could inform decisions about human subject protection and research risk. They may also know and understand more about the issues and disparities the community faces and have ideas of how to be proactive and best address these issues. University and federal review boards should also be encouraged to include American Indian and Alaska Native peoples and researchers to serve on research review bodies, especially when research with American Indian and Alaska Native tribes and peoples have been put forth. This is particularly important in the case of research review in an urban Indian context, where there may not be a formal tribal governance mechanism to provide research review.

Question 29: As noted above, IRBs sometimes engage in activities beyond those that are required by the regulations. For example, an IRB might review some studies for the purpose of determining whether or not they qualify for exemption (the new Excused category), or might review studies involving the analysis of data that is publicly available. Would it be helpful, in furtherance of increased transparency, to require that each time an IRB takes such an action, it must specifically identify that activity as one that is not required by the regulations?

It would be important to use information about the activities IRBs engage in that are beyond those required by the regulations in understanding how that IRB understands its role and regulatory authority. It may also foster coordination across tribal, community-based, regional, institutional, and national research review bodies as part of a more comprehensive initiative to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty. In addition, it may encourage other research review bodies and tribal and community organizations to put forth recommendations that an IRB may consider when it next convenes on issues beyond its regulatory scope.

Question 13: Given the problems with the current system regarding wide variations in the substance of IRB reviews, would it be appropriate to require IRBs to submit period reports to OHRP in the instances in which they choose to override the defaults described in Sections B(1), B(2)(a)(ii), and B(2)(b) above? Should IRBs have to report instances in which they require continuing review or convened IRB review of a study which involves only activities indentified as being on the list of those eligible for expedited review? If an IRB that chose to override these defaults was required to submit a report to OHRP, would this provide useful information about any lack of appropriate consistency among IRBs so that clarifying guidance could be provided as needed, or provide useful information to OHRP about the possible need to revise the expedited review list or the continuing review requirements?

NCAI acknowledges the need to generate an ongoing dialogue across research review boards at the tribal, community-based, regional, institutional, and national levels to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and

reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty. This sort of reporting could contribute to such a dialogue. However, NCAI would also note that this reporting may need to be voluntary as American Indian and Alaska Native tribal governments are sovereign nations who have the authority to impose their own IRB regulations that may be different from federal regulations. They should not be required to report to OHRP if they choose to impose regulations different from federal ones, which require continuing review or convened IRB review of the study or expedited items.

Question 30: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

NCAI recommends that there should not be a requirement for only one IRB of record for multi-site studies, especially when American Indian and Alaska Native tribal nations and peoples are research participants in the study. All participating tribal nations who have active IRBs or review boards should be provided with the opportunity to review the study. If tribal nations choose to defer to one IRB for a multi-site research study of which they are participants that is their option. However, there should not be any mandate for one IRB of record for multi-site studies because local tribal IRBs and research review boards have unique knowledge about a community's history that is important to consider. Therefore, a tribal nation IRB might have different and/or more restrictive guidelines than the federal guidelines. In order for successful collaboration and trust of research studies with American Indian and Alaska Native tribal nations, tribal sovereignty should be respected and tribal government IRBs should be provided the opportunity to review multi-site research studies.

However, NCAI reiterates its acknowledgement of the need to generate an ongoing dialogue across research review boards at the tribal, community-based, regional, institutional, and national levels to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty. This will aid researchers who have to coordinate across several research review boards – and where some of their efforts may be duplicated – as part of multi-site studies because there is not enough coordination on the part of research review boards themselves.

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's specific perspective or knowledge of an institution's specific perspective or the needs of their population, or that a centralized IRB may not share an institution's views or interpretations on certain ethical issues?

NCAI holds that a local tribal IRB or research review board is vital to the review process because these committees generally consists of members from the community or those that are actively engaged in the best interests of the community. Local IRBs add to the protection of research participants through an understanding of the unique knowledge of local context, including history of research in tribal community and past harms resulting from research – about which nearly every American Indian and Alaska Native tribal nation would have stories.

Historically, federal IRBs do not have adequate representation of tribal members as evidenced by the creation of the American Indian and Alaska Native Health Research Advisory Council.

Question 33: How significant are the inefficiencies created by local IRB review of multi-site studies?

Although there may be inefficiencies with multiple IRB reviews or local tribal IRB review along with a university review, the benefit of research participant protection is worth the extra time and process. When it comes to research with American Indian and Alaska Native tribes and peoples, NCAI advocates that it is better to have a thorough review of a research study by a tribal IRB than to rush the process without community or tribal involvement. Not having local IRB review increases the risk of harm to research participants later in the project, when effects are irreversible as occurred in the *Havasupai Tribe v. Arizona Board of Regents*.

Question 34: If there were only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of "IRB shopping" – intentionally selecting an IRB that is likely to approve the study without proper scrutiny – be prevented?

NCAI recommends that if only one IRB of record is allowed for multi-site studies with American Indian and Alaska Native tribal nations, that the study team be required to use the tribal IRB as the one of record. Alternatively, the research team could submit their research proposal to a university IRB in addition to, but not in place of, an application to a tribal IRB. Allowing the option for only one IRB of record could allow some researchers to engage in "IRB shopping" and bypass tribal research regulation processes in order to avoid community involvement in publications, ownership of data, and data analyses.

NCAI reiterates its acknowledgement of the need to generate an ongoing dialogue across research review boards at the tribal, community-based, regional, institutional, and national levels to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty. This may work to prevent inconsistencies across research review processes that contribute to "IRB shopping".

F. Informed consent should be required for all studies and standardized, general consent forms should be avoided.

Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as public education campaigns combined with a notification and opt-out process?

NCAI recommends that a standardized general consent form should not be used. "Blanket consent" or general consent was used in the *Havasupai Tribe v. Arizona Board of Regents* case and harm resulted. NCAI recommends specific informed consent forms which detail how specimens and data can and will be collected and used. All secondary uses of collected specimens and data should require an additional consent process. Informed consent forms should also be clear, understandable, and specific enough to ensure an informed consent can be solicited. NCAI also recommends that options be provided for research participants on informed consent forms (e.g., checkboxes for what types of research they do and do not want their data

used for) to ensure a clear, full-disclosure process. The Belmont Report's principles of autonomy and respect for persons require honoring decisions and wishes of research participants, rather than blanket use of their specimens and data without their explicit consent for specific purposes. Many American Indian and Alaska Native peoples believe that specimens and blood are considered are sacred as they contain a person's essence and spirit. For this reason, sharing specimens between investigators or moving them from facility-to-facility is worrisome and spiritually concerning for tribal nations and peoples. By providing a full detailed informed consent form, tribal participants will have the option to determine how their specimens and data can be used.

NCAI reiterates its acknowledgement of the need to generate an ongoing dialogue across research review boards at the tribal, community-based, regional, institutional, and national levels to clarify issues of responsibility for protection of human subjects; oversight authority; application expectations and reporting requirements for investigators; and how research review regulation coordination serves to protect and advance tribal sovereignty. Tribal consultation on informed consent processes will be important as part of any decision-making about standardizing consent forms and generating best practices in the context of research with American Indian and Alaska Native tribes and peoples.

Question 50: What is the best method for providing individuals with a meaningful opportunity to choose not to consent to certain types of future research that might pose particular concerns for substantial numbers of research subjects beyond those presented by the usual research involving biospecimens? How should the consent categories that might be contained in the standardized consent form be defined (e.g. an option to say yes-or-no to future research in general, as well as a more specific option to say yes-or-no to certain specified types of research)? Should individuals have the option of identifying their own categories of research that they would either permit or disallow?

As noted in our response to question 49, NCAI recommends that all secondary uses of collected specimens and data should require an additional consent process. Additionally, clearly defined choices or checkboxes should be incorporated into the informed consent form for participants to specify which types of studies and how they would or would not like to participate. With respect to the last subquestion, individuals should have option to identify their own categories of research they would permit or disallow. The ability of participants to self identify their own categories of research they would permit or disallow should be clearly explained and defined in the informed consent process. However, NCAI cautions against using consent processes to garner blanket consent before future and secondary aspects of research design and data use have been determined. While many members of the general population may have a better sense today than in past about research and their rights, researchers and research review bodies should not transfer responsibilities around consent processes to potential participants. Researchers and research review bodies have significant responsibilities to ensure consent processes are informed and that human subjects are protected throughout the entire research process.

Question 51: If the requirement to obtain consent for all research uses of biospecimens is implemented, how should it be applied to biospecimens that are collected outside of the U.S. but are to be used in research supported by a Common Rule agency? Should there be different rules for that setting, and if so, what should they be? Should they be based on the relevant requirements in the countries where the biospecimens were collected?

NCAI recommends that the requirements of individual countries be followed for specimens and data collected outside the United States. However, if those countries do not have regulations or standards, then the minimum ethical requirements adhered to in the United States should still be followed. The sovereignty of international governments should be respected, just as tribal nations' sovereignty is important to consider in research regulation. NCAI requests and recommends that the new OHRP regulations specifically include language that explicitly recognizes the value of local American Indian and Alaska Native tribal nation review in all research projects. Implementing this specific language in the new IRB regulations will help researchers to understand that both international governmental sovereignty and American Indian/Alaska Native tribal sovereignty impact research regulation and review processes.

G. The proposed data protections will help prevent harm to research participants and tribal communities.

Question 54: Will use of the HIPPA Privacy Rule's standards for identifiable and de-identified information, and limited data sets, facilitate the implementation of the data security and information protection provisions being considered? Are the HIPPA standards, which were designed for dealing with health information, appropriate for use in all types of research studies, including social and behavioral research? If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?

NCAI supports the use of HIPAA Privacy Rule standards for identifiable and de-identifiable information and data sets. For some social and behavioral research, individual participants may wish to be identified to "receive credit" for their contribution. In these cases, the informed consent form should explicitly have the option for participants to be identified or not be identified.

Questions 59: Would study subjects be sufficiently protected from informational risks if investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules? Are such standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research? Or might a better system employ different standards for different types of research? (We note that the HIPAA Rules would allow subjects to authorize researchers to disclose the subjects' identities, in circumstances where investigators wish to publicly recognize their subjects in published reports, and the subjects appreciate that recognition.)

As noted above, NCAI supports the use of HIPAA Privacy Rule standards for identifiable and de-identifiable information and data sets will help with data security. These standards are appropriate for most types of research studies and data. Employing different standards for different types of research could be confusing and lead to inconsistent application of those rules.

Question 56: DNA extracted from de-identified biospecimens can be sequenced and analyzed in other ways, with the results sometimes being linked to other available data than may allow a researcher to identify the persons whose specimens were being studied. How should Federal regulations manage the risks associated with the possibility of identification of such biospecimens? Should a human biospecimens be considered identifiable in and of itself? What are the advantages and disadvantages of considering all future research with biospecimens to be research with identifiable information?

NCAI recommends that DNA and biospecimens should be considered identifiable in and of themselves because genome sequencing technology is making it more possible to link DNA with an individual. As noted above, NCAI is concerned about secondary use of data, so rigorous data protections should be applied to genetic information and specimens containing DNA. As noted above, NCAI advocates specific informed consent be required for all studies in which an individual's DNA or data are used, and that general informed consent not be allowed.

Question 63: Given the concerns raised by some that even with removal of the 18 HIPAA identifiers, re-identification of de-identified datasets is possible, should there be an absolute prohibition against re-identifying de-identified data?

NCAI recommends there should not be an absolute prohibition from re-identifying data sets that were previously de-identified. Sometimes it is necessary to link back to individuals to share with them test results found in research related to their health. There may also be a future need to go back to individuals for new informed consent for secondary use of specimens and data in future studies.

Question 64: For research involving de-identified data, is the proposed prohibition against a researcher re-indentifying such data a sufficient protection, or should there in some instances be requirements preventing the researcher from disclosing the de-identified data to, for example, third parties who might not be subject to these rules?

NCAI recommends there should be a prohibition on sharing data sets with third parties, regardless of whether they are subject to the HIPAA rules or not. Sharing data sets with individuals outside the original research team is very concerning to NCAI given the *Havasupai Tribe vs. Arizona Board of Regents* case. Sharing of this information is fine if tribal or individual participant consent is given but such tribal government consent should be sought and required in the new regulations.

H. Consultation on IRB regulations with American Indian and Alaska Native tribal nations is vital for any future data collection by the federal government regarding local IRB review and approval and human subjects protection.

Question 68: With regard to data reported to the Federal government: a. Should the number of research participants in Federally funded human subjects research be reported (either to funding agencies or to a central authority)? If so, how? b. What additional data, not currently being collected, about participants in human subjects research should be systematically collected in order to provide an empirically-based assessment of the risks of particular areas of research or of human subjects research more globally? c. To what types of research should such a requirement apply (e.g., interventional studies only; all types of human subjects research, including behavioral and social science research)? In addition, are there other strategies and methods that should be implemented for gathering information on the effectiveness of the human subjects protection system?

NCAI acknowledges that it may be helpful to collect more data about participants in human subjects research, including number of participants being reported to a central authority. NCAI also agrees that it may also be helpful to collect data on adverse events for central database. However, NCAI recommends that before any such data collection is mandated or conducted,

there should be formal consultation with tribal governments under the tribal consultation policy. American Indian and Alaska Native tribal nations are sovereign governments and are often reluctant to engage in research studies and share their data when there has not been prior consultation about the research process. For more information on NCAI's recommendations for effective federal data collection in American Indian and Alaska Native communities, please see the white paper, "Federal Data Collection in American Indian/Alaska Native Communities." For a copy of the paper, please contact Emily White Hat, Program Manager, at ewhitehat@ncai.org.

Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subjects protections. Towards that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?

Empiric data on adverse events in research studies would be a helpful resource. In particular, having such data sorted by study population, with separate data collected explicitly from research studies including American Indian and Alaska Native communities, would be very useful. However, as noted above, any such data collection should be preceded by formal consultation with American Indian and Alaska Native tribes, which have a government-to-government relationship with the federal government. The DHHS American Indian and Alaska Native Health Research Advisory Council (HRAC), which includes tribal leaders from diverse regions, would be an excellent resource for beginning such consultations.

I. Other Issues

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently.

NCAI recommends that the list of research activities that can qualify for expedited review should take place every two to five years.

Question 71: Should the applicability of the Common Rule be extended to all research that is not Federally funded that is being conducted at a domestic institution that receives some Federal funding for research with human subjects from a Common Rule agency?

NCAI recommends that protections provided to research participants under the Common Rule should be applied to all research projects not just federally funded studies. Establishing a standard for research protections regardless of the funding sources helps to prevent harm to research participants.

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally? Would a single set of guidance be able to adequately address human subjects protections in diverse populations and contexts, and across the broad range of research context (including biomedical, national security, education and other types of social and behavioral research)?

NCAI recommends coordination between federal agencies on regulations regarding the protection of research participants. A single guidance document would be helpful and would help to ensure consistency in protections for research participants. NCAI also recommends formal

consultation with American Indian and Alaska Native tribal nations before such a guidance is developed. Tribal consultation would help ensure that the unique concerns and contexts of tribal nations are included in the guidance document. Different types of research may involve unique considerations as well. However, a single guidance document could include such exceptions where they may exist (e.g., for surveys or interviews as used in education or behavioral research) while still including a uniform minimum ethical standard for all types of research.

III. Conclusion

Thank you for the opportunity to provide comments. NCAI recommends formal tribal consultation on the proposed IRB regulation changes because they are significant and will have lasting effects on the integrity of research with American Indian and Alaska Native tribal nations. Consultation with tribal nations should be held in a manner consistent with the Department of Health and Human Services' tribal consultation policy and on a government-to-government level. NCAI is willing to facilitate such a tribal consultation regarding OHRP's proposed regulatory changes. For more information about these comments, please contact Emily White Hat, Program Manager, at ewhitehat@ncai.org.

[i] http://www.uaf.edu/irb/readings/BAS_Case_Study.pdf