



ASIP Public Affairs

[1999 ASIP Response to NBAC Draft Report](#)

National Bioethics Advisory Commission

"The Use of Human Biological Materials in Research: Ethical Issues and Policy Guidance"

The National Bioethics Advisory Commission released its draft report on the appropriate use of archived human tissues in research on December 3, 1998 for public comment on or before January 17, 1999 (see <http://bioethics.gov/>). Drs. Richard Lynch and Mark Sobel prepared ASIP's response, reproduced below. The Commission is now revising its draft according to responses received and also Commission discussions at their meeting on January 20. It is possible that the Commission may have additional discussion at their February meeting in Princeton NJ. Although the deadline for comments has passed, you may wish to submit your own comments to the Commission.

ASIP Response to Draft Recommendations

"The Use of Human Biological Materials in Research: Ethical Issues and Policy Guidance"

The American Society for Investigative Pathology (ASIP) is an organization of 1600 research scientists who study the mechanism of disease. Approximately half of our members are M.D.s; the other half are Ph.D.s. Many, but not all, of our members are in departments of pathology, and most are in the United States. Our members are active in research and rely heavily on human biological materials for their studies, either on the most basic mechanisms of disease processes, on population-based studies of the prevalence of certain conditions (atherosclerosis, cancer, immunologic diseases, infectious diseases, environmental diseases), and clinically-based studies on the expression of disease in tissue samples related to medical conditions. The latter type of research eventually leads to advances in more accurate prognosis for certain conditions and for measuring the effectiveness of therapies.

ASIP is a signatory to the Pathology Consensus Statement that will be published in *Archives of Pathology and Laboratory Medicine* in **April, 1999**, which is essentially identical to the position paper that the College of American Pathologists has submitted to NBAC previously. ASIP has taken a leadership role in the pathology community to educate its members about the ethical implications of human tissue research and the federal regulations that govern such use in federally funded institutions, and has followed the NBAC deliberations with great interest.

ASIP is gratified that the draft report recognizes the research value of human biological materials in improving the public health. Furthermore, we are pleased that the town meetings that were held under the auspices of the NBAC demonstrated an overwhelming support by the American public for medical research.

Although ASIP agrees with the necessity to protect human subjects and their privacy, and appreciates the huge effort put forth by the NBAC, we are disappointed with some of the draft recommendations. The ASIP response is organized in two parts: (1) general comments and (2) specific comments for each recommendation in Chapter 5.



I. General comments:

- 1. General principles for the use of HBMs.** The need to protect the rights and privacy of human subjects is a central tenet of ethical biomedical research. A balance between the need for privacy and personal rights on the one hand, and the need to permit research to serve the public good on the other hand, should be the goal of all human subject research. Adequate security of all research information is the key to protecting privacy. IRBs play a critical role in determining if research protocols provide adequate protections for human subjects. The IRB should consider the nature of the research proposed on HBMs, whether such research poses a realistic threat to privacy given the way in which the HBM samples will be used (stripped of all identifiers, linked, or frankly identified), and the necessity for or appropriateness of consent.
- 2. Misuse of information.** ASIP is concerned that the Commission has generally established guidelines that will result in major obstacles for researchers to continue to use human biological materials (HBMs) in their research, with a consequent loss of important public health benefits. Risks to human subjects occur not through the gathering of information by researchers, but through the misuse of such information. Obtaining informed consent from human subjects is not a productive or adequate protection. **We urge the Commission to recommend that all repositories of HBMs, including all academic departments that hold human samples, establish IRB approved policies to assure the confidentiality and security of information gathered in research studies.**
- 3. Probability and magnitude of risk.** Although the draft report includes a recognition that there are two scales (probability and magnitude) on which to measure risk to human subjects, this is not adequately elaborated in Chapter 5, thus failing to give proper guidance to IRBs. The Commission is recommending that research using potentially identifiable HBMs not be exempt from IRB review, including linked (coded) samples, even when the researcher does not have ready access to the key of the code, or has no intention to break the code. The probability that a risk might occur to a human subject from a coded sample is virtually zero, especially if the confidentiality and security procedures that CAP and ASIP have recommended are put into place. Furthermore, even in situations where frankly identified HBMs are utilized in research, the vast majority of research using HBMs involves non-stigmatizing, non-germline research on somatic cell mutations that have no hereditary implications, or other non-genetic traits (*e.g.*, infectious diseases, toxic agents) that are not stigmatizing. In addition, the majority of research studies using HBMs do not employ DNA analysis. The examples given in the draft report to elaborate on recommendations almost exclusively represent high magnitude and high probability situations which do not reflect the majority of HBM research studies.

It is extremely important, indeed essential, that NBAC provide clear guidance to IRBs that clarifies that use of coded HBMs when confidentiality and security policies are in place represents minimal risk to human subjects. The government does not serve the biomedical research community, their human subjects, or their patients well by placing obstacles along the path that leads to a better



understanding of diseases and potential treatments. While it may not be the intent of the Commission to place such obstacles, history tells us that universities and other institutions and IRBs will interpret policies and language in those policies in a very conservative fashion to avoid any perceived violation of the law or to avoid loss of financial support of federal funding. The impact of conservative interpretations will be realized at the level of the patient, the clinician, the research community, and the societal benefits that can come from research with HBMs.

4. **Different types of repositories.** Repositories of HBMs run the gamut from large collections of tissues in dedicated facilities, to pathology departments with collections of HBMs collected during the course of clinical care procedures, to very small collections held by individual investigators. It is not feasible to make broad recommendations concerning the conduct of repositories without taking this variation into account. In the case of HBM archived collections in pathology departments, the Commission does not appear to appreciate that such collections are developed and kept to assure the best possible clinical care for the patient. Research use of such collections is secondary to clinical care issues and is only permissible on excess tissue that will not be required for future re-analysis and for quality control and assessment purposes.
5. **Research on HBMs is essentially different from interventional clinical research and research findings should not be part of the medical record.** ASIP cannot stress strongly enough that research using HBMs should not directly affect the individual human subject and has little potential to do so. **Research findings that are not validated and peer reviewed should not affect clinical care and should not be entered into the medical record unless they meet CLIA standards (which is not relevant to the vast majority of research laboratories).** It is critical to understand that individual research studies must be validated and duplicated before they have medically relevant value. The danger to the public is greater from release of inappropriately validated research data than from withholding such information.
6. **Informed versus simple (general) consent.** Obtaining consent from human subjects to use excess HBMs in research in future studies, in situations where a research study is not yet in place, should achieve the goal of informing patients about potential risks of harm from inadvertent or wrongful disclosure with consequent psychosocial harms or employment or insurance discrimination. **ASIP recommends that such consent should include information that security and confidentiality policies are in place to avoid or minimize such risks.** In addition, ASIP recommends that such consent establish that a patient's failure to agree to future HBM research should not have an impact on availability of clinical care. **ASIP believes that such a simple (general) consent is adequate for the future use of excess HBMs in research.**
7. **Use of HBMs in education and quality control studies.** The draft report does not define whether its recommendations apply to the use of HBMs in education of public health professionals or in quality control studies that are essential for the proper functioning of clinical service laboratories.
8. **Expedited review.** The draft report does not make recommendations as to the appropriateness of expedited review of protocols submitted to IRBs. **ASIP recommends authorization of an expedited review process, either by an administrative Office of Human Subject Research in each institution, or by the Chair and a subcommittee of the IRB, to review protocols utilizing HBMs in which the**



samples are linked but there is no intent on the part of the investigator to identify the samples. This will relieve a tremendous work burden from the IRB and remove administrative obstacles for the researchers. In many of these cases, a determination of minimal risk and no harm to personal rights could facilitate granting of a waiver of informed consent.

9. **Honest broker.** ASIP is disturbed that the tenor underlying the recommendations of the draft report is a basic distrust of the investigator, and an apparent repudiation of the concept of the physician/researcher as an honest broker when HBMs are used in research studies. The medical scientific community has a strong history of protecting patient rights. Despite the collection of millions of specimens over the past century, few evidences of abuse in the use of HBMs that resulted in harm to human subjects have been documented.

10. **Summary of misconceptions.** It appears from the draft report that the recommendations rely heavily on impressions and concerns of the Commissioners rather on data of documented harms to human subjects through the use of HBMs. Assumptions that underlie many of the recommendations, which ASIP feels are not warranted, include: (a) the general public fears having their coded tissues used in medical research; (b) the research studies for which coded HBMs are used is primarily inherited disease genetic research; (c) tissue samples that are coded are readily identifiable by the researcher, repository staff, or others; (d) researchers have ready access to medical records; (e) research results are medical information and are entered into the medical record.

II. Specific comments on recommendations:

ASIP recommends that the recommendations be re-ordered so that recommendations dealing with the same issue are grouped together.

A. Recommendations concerning identifiable samples, and rendering samples unidentifiable.

Recommendation 1. ASIP is concerned that Recommendation 1 considers all coded samples as identified, no matter how impractical, difficult or improbable that might be. This recommendation will increase the workload of already overburdened IRBs throughout the country. ASIP feels that the NBAC should provide clear guidance to IRBs so that they can consider the probability of identifiability when considering risk and potential harms to human subjects when coded HBMs are used in research. Furthermore, ASIP recommends an expedited review process for such coded samples.

ASIP is also concerned with the provision in Recommendation 1 that samples be rendered unidentifiable by someone other than the investigator. This recommendation reflects a suspicion of researchers integrity that ASIP does not feel is warranted by the evidence of decades of responsible research utilizing HBMs. An alternative interpretation is that this recommendation is meant to avoid situations in which an investigator unintentionally retains some memory of the identity of a sample, which is hardly likely given the large number of samples that researchers use in HBM studies. Furthermore, if security and confidentiality policies that have been approved by an IRB are in place, protection should be adequate. Requiring someone other than the investigator to anonymize a sample introduces another layer of risk in that a third



party now has access to the sample, and integrity of the sample may be compromised. The recommendation is also unclear as to whether it applies to the principal investigator or to all research personnel in the laboratory or department.

Recommendation 4. ASIP is concerned that endorsement of the strict interpretation of the current federal regulations (the common rule) that is currently provided by the OPRR should be balanced by clear guidance to IRBs about minimal risk assessments of protocols utilizing coded HBMs, and the circumstances suitable for expedited review.

Recommendation 11. ASIP believes that this recommendation should be deleted and replaced with a simple and clear recommendation that investigators should obtain an exemption from an appropriate institutional official to perform research on anonymized or anonymous HBMs. It defeats the purpose if researchers strip identifiers from HBMs if that would compromise the research. Commentary on the valuable use of coded samples, and ways to strip identifiers, would be useful adjuncts to the actual recommendation, but are best left out of the recommendation itself.

B. Repositories.

Recommendation 2. ASIP agrees that repositories have a responsibility to maintain the safety and security of HBMs in their collections and should not distribute samples for unauthorized research. However, ASIP is concerned that this recommendation does not adequately accommodate the different types and sizes of repositories. In some cases, and consistent with current OPRR guidance, where the collection site IRB and repository IRB have approved the handling of samples, it is neither necessary nor advisable for the individual investigator to provide documentation of IRB approval, since the individual researcher's IRB may not have access to information concerning collection and consent procedures.

C. Group Harms and Pedigree Studies.

Recommendation 3. ASIP strongly endorses the notion that no regulatory oversight is necessary for research using unidentifiable HBMs. Although we also agree that researchers and IRBs should be mindful of potential harm to groups, we believe that statements concerning group harms best belong in commentary and should be included in the ethical perspectives discussed in Chapter 3 of the draft report. ASIP is concerned about the general lack of clarity and specificity for protection against group harms. Since ASIP is proposing that exemptions from IRB oversight be granted by an institutional official (see Recommendation 11 above) for all anonymous and anonymized samples, this should provide adequate opportunity for review by someone other than the investigator.

Recommendation 13. ASIP agrees that investigators should be cognizant of potential harms to individuals who are not the direct subjects of a research study and should design their studies appropriately. We strongly concur that no research results that could lead to the identification of an individual should be published without adequate, specific, informed consent and we believe that journals already abide by this prohibition. However, ASIP believes that the wording of recommendation 13 is imprecise, confusing, and duplicative (see also Recommendation 16). Recommendation 13 should be deleted, and the general point should be moved to a commentary section. At the very least, individual members who are the sample



source are subject to the same potential harms as other individual members of that family or group, so that risk and harm will have been considered by the IRB.

D. Criteria for Waivers of Consent, Adequacy of Consent and Recontact.

Recommendation 5. ASIP strongly concurs that the practicability requirement be dropped when considering waivers of consent for research on identifiable samples, as long as the research is determined to be of minimal risk and that there are no adverse consequences relevant to subjects rights and welfare. Since this would require a change in the federal guidelines, in the meantime, ASIP suggests that NBAC provide guidance to IRBs that the practicability requirement be considered of lesser weight than assessment of risk and rights and welfare. ASIP suggests that the wording of Recommendation 5 can be improved. The last sentence is a non sequitur and is unnecessary. The IRB should first determine minimal risk and no harm to the rights and welfare of the subjects. Only when these criteria are met should the practicability requirement be dropped. ASIP further suggests that the NBAC recommend deletion of the fourth criterion for a waiver of consent (whenever appropriate, the subjects will be provided with additional pertinent information after participation) in research studies using HBMs, since we strongly believe that research results that are not validated and peer reviewed should not be provided to research subjects without adequate counseling as to their speculative and unscientific nature.

Recommendation 7. ASIP agrees that IRBs should have the authority to approve, disapprove, or require modifications of research protocols. We disagree with the last sentence of recommendation 7 and suggest it be deleted.

Recommendation 8. ASIP agrees with the concept of recommendation 8 however the wording is confusing and internally duplicative. Furthermore, the discussion preceding this recommendation (see page 145 of the draft report) indicates that most existing consent forms are inadequate for inferring consent to future research. Therefore, recommendation 8 would, in effect, require recontact of sample sources to obtain new consent, a process that is neither practicable or necessary in our opinion. ASIP recommends alternate wording: When an IRB determines that the requirement of informed consent cannot be waived and that any existing consent document is insufficient to permit an existing identified sample to be used in the study, subjects may be offered the following options: 1) consenting to the specific proposal and or 2) giving authorization for future (unspecified) research use of the sample.

Recommendation 10. ASIP believes that this recommendation confuses two separate issues that are not adequately addressed. Recontact to prospectively inform subjects about research (to provide options for participation as in recommendation 8 above) is distinct from recontact to divulge research results (see our comments in recommendation 5 above). ASIP strongly agrees that IRBs should have the authority to require recontact when it does not grant a waiver of consent, but ASIP is gravely concerned about inappropriate recontact to divulge research results that are not validated and reproduced.

Recommendation 12. ASIP agrees that the consent process for use of HBMs should be improved and that a separate consent for research is preferable. Consent forms that are geared toward clinical care are not well suited for research on HBMs since the latter does not involve patient therapy or active intervention. Participation in research is driven by altruistic values and it should be clear to subjects that it will not



affect their clinical care. ASIP strongly recommends a simple separate general research consent process. We further recommend that however simple a consent process is, that subjects be informed that they have the right to refuse participation in research and that such refusal should not compromise their clinical care.

E. Sensitive or Objectionable Research.

Recommendation 6. ASIP believes that the wording of this recommendation is unclear and confusing. The issue of whether research is objectionable on any grounds, including moral, should be considered by the IRB when assessing minimal risk and rights and welfare of subjects and is already covered by the regulations. In such circumstances, consent should not be waived. However, once the IRB has determined that consent is required, ASIP believes that the IRB should have the prerogative of recommending an opt-out consent process where practicability issues are problematic.

Recommendation 7. ASIP believes that this recommendation is duplicative to recommendations 6 and 8 and should be deleted. Any requirement to recontact sources of specimens should be made only after serious consideration of the costs, practicability, and psychological risks to the subjects.

F. Improving Education and Publication Guidelines.

Recommendation 14. ASIP strongly endorses the responsibility of scientific and medical organizations to develop guidance for their membership, and has taken a leadership role in that process.

Recommendation 15. ASIP strongly endorses efforts by OPRR to improve the education of IRBs, the research community and repositories.

Recommendation 16. ASIP concurs with the spirit of this recommendation but suggests alternate wording: When submitting research for publication, investigators should be asked by journal editors to indicate that research studies using HBMs were conducted in compliance with the rights and welfare of human subjects. To specifically require prior approval by an IRB, when unidentified samples are used, or even in the absence of federal funding, would be an inappropriate overextension of federal regulations.