IHS Guidelines for implementing and complying with IHS Policy on specimens

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I. Objectives

The objectives of these IHS Guidelines are simultaneously to:

support fully informed Tribal and IRB review and approval of research that will save specimens for future research, or that will use saved specimens;

support fully informed consent by each potential volunteer participant of the research that obtains specimens to be saved;

support future use of specimens that is based both on the merits and soundness of the science, and by the concerns and health priorities of the Tribe[s] involved; and

support the proper obtaining, retention and use of saved specimens that observe the limits and intents of the informed consent by the people from whom the specimens were obtained, and of the approval by the IRB[s] and Tribal government[s].

II. The IHS Guidelines

[1] All researchers who obtain or use, and all entities that store, specimens obtained with IHS involvement must agree to these Guidelines. IHS will distribute to researchers, specimen banks, and IRBs both the Guidelines and model consent forms for specimens.

[2] If blood or tissue will be obtained directly from volunteer participants under a research protocol, both the protocol and its consent process and form must specify:

- the tests to be done under the protocol;
- if any specimens will be saved.

[3] If any specimens will be saved, both the protocol and consent form must state the nature of future "secondary uses," and the process to seek approval of the future uses:

- whether the stored and maintained specimens will included identifiers;
- class[es] of tests or procedures that may be done on the saved specimens, including DNA tests, or other genetic tests, or growth of perpetual cell lines;
- if volunteer participants may be contacted in the future by the PI or other researchers;
- location, duration, and procedures of storage and of disposal;
- if the specimens are from placenta or umbilical cord, other tissues with strong social meaning or value, or other aspects about which the AI/AN community may be concerned, e.g., patenting specimens or material derived from them.

[4] The researchers of the original protocol must not permit others to engage in, and must not themselves engage in, secondary use of specimens until they comply with all steps. "Secondary use" includes the following:

- tests or other uses not explicitly mentioned, either by name or as a class, in the original protocol and consent; or
- giving or loaning specimens to anyone else. (This does not include other laboratories doing allowed tests for the original researchers; it does include laboratories retaining specimens or doing their own tests.)

[5] Researchers of the original protocol, and of a new protocol receiving specimens, must track and comply with the limits on the use of each specimen imposed by the consent of the person from whom it was obtained, even if the specimen is anonymous or if the person from whom the specimen was obtained has died.

[6] All proposed secondary uses of specimens must be reviewed for scientific value by an independent group. The original protocol that stored the specimens must include such review and approval in its procedures. As a nonrenewable resource, specimens should be used up only by research with high scientific value; scientists other than the researcher should judge the scientific value of the proposed use. Specimens also must not be hoarded (to benefit a researcher's career, for instance) but must be shared if it benefits a volunteer or family, Tribe, or society. Those two obligations are especially important for specimens not easily obtained, e.g., by surgery or biopsy.

[7] All proposed secondary uses of specimens must be reviewed and approved by the Tribal government[s] with jurisdiction. The original protocol that stores specimens must include such review and approval in its procedures.

[8] All proposed secondary uses of specimens must be reviewed and approved by all participating institution that hold, send, or receive the specimens, using their SPA IRB or MPA procedures. The researcher of the new protocol must send the consent forms under which the specimens were originally obtained with the protocol for review.

[9] Many "anonymous" specimens have clinical or demographic information about the people from whom the specimens were obtained. IRB review must assess if true anonymity is achieved and maintained, i.e., that identification of some people cannot occur due to combination of demographic or clinical data or linkage to other databases.

[10] If all proposed uses are within the original truly informing consent, see **Table 1**. Within the original truly informing consent means the consent cited the uses as a class (e.g., "kidney function tests") or by name. Related to original study means the stated purposes for which the specimens were obtained. (These two criteria may be different; see Section III, Additional information.) Proposed uses are exempt from further IRB review if they are within the original consent, and related, and anonymous; the determination that they meet all three criteria is by the institution's MPA procedure or SPA IRB, not by the researcher. All other proposed uses within the original consent require "expedited" or full IRB review.

TABLE 1

When all proposed uses of specimens are within the original truly informing consent:

Related to original study	Anonymous	Standard conditions for the new research protocol or plan:
yes	yes	Scientific merit review and approval (i.e., "review, then either approval or veto, of the protocol"); and each institution's review and approval; and notification of Tribe; and publications identify the community only with Tribal consent.
yes	no	Scientific merit review and approval; and IRB review and approval of the protocol's modification; and notification of Tribe; and researchers not contact individuals without their consent; and publications identify the community only with Tribal consent.
no	yes, or no	Scientific merit review and approval; and IRB review and approval; and formal Tribal review and approval; and informed [re]consent by each volunteer participant, unless excepted by the IRB for anonymous specimens; and publications identify individuals only with their consent; and publications identify the community only with Tribal consent.

[11] Proposed uses may be outside the original consent, usually for one of three reasons.

The original consent did not include future use at all.

The original consent was too broad--a blanket consent to do any test--and thus was not truly-informing by today's standards. (These two consents are frequent in clinical care or older research.)

The future use is beyond a reasonably detailed truly-informing consent.

Future possible uses or protocols are so varied that a table of standard conditions is not feasible. Every proposed use must be approved by all Tribe[s] and IRB[s] involved, and by an independent scientific group.

[12] Many new tests, like genetic tests, require pre-test counseling. If the protocol will do new tests with clinical relevance to people from whom the specimens were obtained, and if the specimens are identifiable, the researchers must specify how and when they will obtain the informed consent of each person to receive--or to not receive--the test results. (Many new tests are not CLIA approved; generally the results of non-CLIA approved tests are not given directly to the volunteer participants or their physicians.)

[13] The entities retaining specimens, and PI and co-investigators of every protocol, that obtain, store, test, or use the specimens must sign a copy of one of the following. The signed agreements extend these Guidelines to laboratories, specimen banks, and researchers that receive, hold, test, or secondarily use any specimens; the original researcher must obtain the same written agreement from them. The originals are sent to the IRB[s] and Tribe[s] involved. If the new protocol is receiving specimens for secondary use, copies of the signed forms are sent to the original researcher.

All researchers will comply with the following for specimens and data in this project:

1. *NOT use the specimens and data received for any purpose other than those stated in this protocol and approved by the Tribe[s] and IRB[s];*
2. *NOT release the specimens, or their associated raw data, to any other person or study, without the prior approval by the IRB[s] and Tribe[s] involved;*

3a. *If the specimens or data are supposed to be anonymous, NOT attempt in any way to establish the identity of the subjects of the specimens or data received.*

3b. *If the specimens are not anonymous, NOT try to contact any individual or family other than as stated in this protocol, without the prior approval by the IRB[s] and Tribe[s] involved.*

3c. *If the specimens are not anonymous, NOT try to obtain clinical or other information from anyone's medical or other records other than as stated in this protocol, without the prior approval by the IRB[s] and Tribe[s] involved.*

[14] Storage of all specimens must provide physical security from unauthorized or inappropriate access. The disposal of specimens must be respectful.

[15] Researchers of the new protocol to use existing specimens have the same obligations as do the researchers of the original protocol. Those obligations generally include:
to present the results of the research to the Tribe[s] involved; and
to seek Tribal review of publications.

[16] Research teams must insure "institutional memory" to comply with requirements after the PI has left. Research teams should also have written agreements with their institutions to define control and responsibility over the storage and disposition of the specimens. The Tribe[s] and IRB[s] involved may need to know those agreements.

[17] IRB[s] and Tribal government[s] may notify funding agencies, supporting institutions, and publishers or editors of violations of these Guidelines that are not resolved.

[18] These Guidelines must be re-examined, and may be modified, as experience develops.

III. Discussion

The IHS has five special considerations, circumstances, and concerns.

Confidentiality and anonymity are more difficult to maintain in small rural communities, as are most IHS sites, than in large urban areas.

Because clinical care data in the IHS are computerized, true anonymity is difficult to achieve, due to possible combinations of computerized clinical data elements.

AI/AN communities have been stigmatized by recent research, which reinforces the fears and distrust that many AI/AN and other people have about research.

Many AI/AN people have special cultural values and concerns related to the use of blood and other tissues.

Tribal governments legally control research done within their jurisdiction. IHS Guidelines must work with each Tribe's Codes and procedures to control research.

Secondary research on blood or tissue specimens is increasingly sophisticated and frequent. Such research may have future benefit to the people and communities whose specimens are tested. For specimens that both are anonymous and exist before the research use, 45 CFR 46 § 101(b)(4) permits research on them without the informed consent of the people from whom they were obtained, because the research appears to carry no risk to them even if the tests are sensitive. However, individual members of a community may be harmed even though the specimens are "anonymous for individuals," if the specimens retain the community's identification or are known to come from that community. The community at risk may be a specific Tribe, a group of Tribes (e.g., "Tribes in the Northwest"), or ethnicity (e.g., "American Indians"). Specimens for which IHS was or is involved in the collection or storage are not anonymous for community because they are known to be from AI/AN people, with the group of Tribes also known. In the IHS policy, therefore, "anonymous" specimens means "anonymous only for individuals"; the specimens are identifiable for the larger AI/AN community at least.

The term "anonymous for individuals" means that it is impossible for the researcher to identity individuals either:

directly (e.g., by name); or
by a combination of data elements.

The term also means that it is impossible for the researcher to identify individuals either:

from only the data at hand; or
with other information (e.g., medical records) to which the researcher has access; or
with information from other people (e.g., people who have access to medical records).

For specimens to be anonymous for the individual, therefore, the researcher must neither have any data, nor have access to any data with the possible cooperation of others, that alone or in combination identify one or more people from whom the specimens were obtained.

A special consideration applies once specimens are in <u>research</u>, i.e., specimens either obtained directly from volunteer participants under a research protocol, or gathered originally by a process of care and now obtained under a research protocol. The original IRB[s] must review and approve every modification of a protocol, by either expedited or full review; see 45 CFR §s 46.103(b)(4) and 46.110. Later activities modify the research protocol, if they were not stated in the original protocol. Such activities include: giving or lending the specimens to another researcher; using them for tests other than those in the obtaining protocol; or seeking a patent. The original IRBs, therefore, must review and approve such activities as <u>modifications to the original protocol</u>. The IRBs must also determine if the proposed modifications are within the limits of the original informed consent.

There are three basic approaches for informed consent to store specimens.

[1] One approach is a blanket consent, that permits all future uses of specimens. It maximizes future testing and flexibility, which benefits future progress in science; however it does not recognize possible harms to communities or individuals, e.g., tests for stigmatizing conditions. For example, a protocol and consent form that leftover blood will be stored for "future tests about diseases of importance to AI/AN people" is a blanket consent. It covers too much, from otitis media to alcoholism, from non-stigmatizing to highly stigmatizing conditions. Potential participants being asked to consent to such future use would be <u>un</u>informed about the risks and benefits.

[2] Another approach is a detailed consent. At the time the specimen is obtained, each volunteer participant decides whether to permit saving a specimen, what future tests can and cannot be done, and whether to be contacted about results of future tests. The approach maximizes participant control; however the control is exercised when participants lack needed information about the future. That is, detailed consent has three major problems: future tests are too unknown and too varied to list; risks and benefits in the future may differ from those at present; and the current circumstances and values of potential volunteer participants may change in the future, rendering a decision based on current circumstances and values invalid for that future person.

[3] These Guidelines take a third approach. Each participant decides to permit or not only future use *related to the current research* to which s/he is consenting--uses with values, risks, and benefits likely similar to those of the current research. For instance, consent about specimens left over from in a vaccine trial would ask for narrow future uses, e.g., "future tests about infections important to AI/AN children." As a check, the Tribes and IRBs must also approve all future uses when they are proposed. As a second check, if the future tests use identifiable specimens for purposes beyond the original consent, the volunteer participants may be asked for consent for the new use.

Five examples will help clarify Table 1. Consider sera from a community project screening adults for diabetes (DM), stored with identifiers; the consent permitted future tests to help diabetes or related conditions such as atherosclerotic heart disease or chronic renal failure.

[1] First row. Researchers want to use the sera (but anonymized), to determine the prevalence in the Tribe of a newly found risk factor for DM.

[2] Second row. Researchers want to run the same test on the same sera but with identifiers, to match results with each person's chart whether or not they have DM.

[3] Third row--anonymous, direct public health implications to the Tribe: CDC wants to test the sera anonymously for antibodies to a newly-discovered fatal infection that broke out in the Tribe, to see if there have been subclinical infections in the past. (The Tribe and IRBs must approve the research; reconsent will not be not necessary.)

[4] Third row--anonymous, disease of small importance to the Tribe. Researchers want to test anonymously for the prevalence of a possible new Alzheimer disease gene in this Tribe with rate of Alzheimer disease one-tenth the U.S. rate, to see if the gene also is less prevalent. (The requirements are the same as for [4].)

[5] Third row--with identifiers, disease of great importance to the Tribe. A new blood test to detect early cancer of the cervix has been proven in non-AI/AN women but not in AI/AN women. Researchers want to run the test on the same stored sera, and get from each women's chart who had cervical cancer. The Tribe's rate of cervical cancer is 10 times the U.S. rate. (The Tribe and IRBs must approve the research; reconsent by each volunteer participants may be necessary. It may be possible, however, to link clinical information about cervical cancer to specimens without seeking reconsent while satisfying the concerns and requirements of the Tribe and IRBs.)

PLEASE GIVE COMMENTS, SUGGESTIONS, OR CRITIQUES TO:

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