

# **IHS GUIDELINES FOR IMPLEMENTING AND COMPLYING WITH IHS POLICY ON SPECIMENS**

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## **I. Objectives**

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 people have about research.
- Many AI/AN people have special cultural values and concerns related to patenting of genes, cloning, and 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.

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 concerns and health priorities of the Tribe[s] involved, and on the merits and soundness of the science; 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 research involving Tribes must have Tribal approval. "Tribal approval" means a resolution by the Tribal Council or by an authority delegated by the Council.
- [2] 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.
- [3] 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.

- [4] 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 include 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 the PI or other researchers may contact volunteer participants in the future;
  - 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 Tribal members may be concerned, e.g., cloning, patenting specimens or material derived from them.
- [5] Researchers must not engage in, and must not permit others to engage in, secondary use of specimens until they comply with all steps. "Secondary use" includes:
- 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. (Giving or loaning specimens does not include another laboratory doing tests for the original researcher, if tests and laboratory were stated in the protocol. It does include other laboratories doing their own tests, doing new tests for the researcher, or retaining specimens.)
- [6] The Tribe[s] with jurisdiction must beforehand: A] at least be notified about all proposed secondary uses that are within the original consent and related to the research purpose; and B] review and approve all other uses. The original protocol that stores specimens must include such notification, and review and approval, in its procedures.
- [7] 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 IRB[s] and Tribe[s], and by the consent of the person from whom it was obtained, even if the specimen is anonymous or if the person has died.
- [8] Proposed secondary uses of nonrenewable 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. Nonrenewable specimens should be used up only by research with high scientific value. 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. Scientists other than the researcher should help judge the scientific value of the proposed use. Those two obligations are especially important for specimens not easily obtained, e.g., by surgery or biopsy.
- [9] All proposed secondary uses of specimens must be reviewed and approved by all participating institution that hold, send, or receive the specimens, using their IRB or Human Research Protection (HRP) procedures. The new protocol researcher must send copies of a consent form, and of the Tribal and IRB approvals, of the original protocol with the submission of the new protocol for review.

[10] 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 identifying some people cannot occur due to combination of demographic or clinical data or linkage to other databases.

[11] 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 criteria may be different; see § III, Discussion.) Proposed uses are eligible for expedited IRB review as a minor modification of the protocol if they are within the original consent and related; the IRB itself or institution's HRP procedure, not the researcher, assesses that they meet both criteria. All other proposed uses within the original consent require full IRB review.

**TABLE 1**

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

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

[12] 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 outside the original consent 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.

- [13] 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. (Some 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.)
- [14] 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 the following. The signed agreements extend these Guidelines to laboratories, specimen banks, and researchers that receive, hold, test, or secondarily use any specimen; the original researcher must obtain the same written agreement from them. The original agreements 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.*

*The researchers understand and agree that noncompliance with this signed agreement will mean at least that the researchers should not publish or disseminate results of the research, and that the IRB[s] or Tribe[s] will notify relevant institutions, journals, publishers, and conferences of the noncompliance.*

- [15] Storage of all specimens must provide physical security from unauthorized or inappropriate access. The disposal of specimens must be respectful.
- [16] 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.
- [17] Researchers must report all secondary uses, and status, of specimens in the Annual (Periodic) Re-Review to the IRB[s].

[18] 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.

[19] 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.

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

### **III. Discussion**

Secondary research on blood or tissue specimens is increasingly sophisticated and frequent. It may benefit in the future 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 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 usually identifiable for the larger AI/AN community at least.

The term "anonymous for individuals" means that it is impossible for the researcher to identify 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.

Many people fear that their specimens will be used in cloning. Cloning requires a live fresh human cell, to put that cell's nucleus into an ovum (woman's egg) to become a baby. Usual blood draws and specimens do not have or keep living cells; the nucleus of a perpetual cell is not fresh. Neither routine blood draws, specimen collections, and perpetual cell lines can be used to make a clone; thus consent documents need not state that they will not make clones.

A special consideration applies once specimens are in research, i.e., specimens either obtained directly from volunteer participants under a research protocol, or gathered originally by a

process of care and now 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 §§ 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 listed in the obtaining protocol; or seeking a patent. The original IRB[s], therefore, must review and approve such activities as modifications to the original protocol; the IRBs must also determine the potential harms of the proposed modifications, and if they are within the limits of the original informed consent.

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

- [A] 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 uninformed about the risks and benefits.
- [B] Another approach is a detailed consent: when the specimen is obtained, participants decide 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. Detailed consent has three major problems: future tests are too unknown and too varied to list; future potential harms and benefits 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 the same person in the future.
- [C] 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 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 to re 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--anonymous. Researchers want to use the sera (but anonymized), to determine the prevalence in the Tribe of a newly found risk factor for DM.

- (2) First row--not anonymous. Researchers want to run the tests on the same sera but with identifiers, to match results with each person's chart whether or not they have DM.
- (3) Second row--anonymous, important to public health of 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; re consent is not possible due to anonymity.)
- (4) Second row--anonymous, without public health importance. Researchers want to test anonymously for the prevalence of a possible new Alzheimer disease gene in this Tribe with a rate of disease 1/10 the U.S. rate, to see if the gene also is less prevalent. (Because the specimens are anonymous, the requirements are the same as for [3]. The Tribe could decide to not allow the research, due to its low importance to the Tribe.)
- (5) Third row--with identifiers, with public health importance. 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; re consent by each volunteer participants may be necessary. It may be possible, however, to link clinical information about cervical cancer to specimens without seeking re consent while satisfying the concerns and requirements of the Tribe and IRBs.)

NOTE: These Guidelines were developed with both formal and informal counsel and input by Tribes, Tribal IRBs, Area Indian Health Boards, and the National Indian Health Board.