Chapter 5
Current Guidance on the Use of Human Biological Materials in Research

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The current landscape of rules and guidelines affecting the use of human biological samples in research includes existing federal regulations in the U.S., policies developed by domestic scientific and professional societies, and guidelines developed by other countries and international organizations. When NBAC began to review the use of human biological materials in research, the work of a number of these organizations provided an understanding of the range of positions that exist among organizations that have carefully considered this subject. This chapter describes NBAC's interpretation of the existing federal regulations, existing policies developed by scientific and professional societies, and international efforts to address the topic.

A BRIEF HISTORY OF HUMAN SUBJECTS PROTECTIONS

The modern story of human subjects protections begins with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis.[1] The Code captures many of what are now taken to be

[1] Several excellent sources trace the history of human subjects research and the development of the IRB system as a mechanism for the protection of human subjects. An account of the history of human subjects research and the human subjects protection system in the United States can be found in David J. Rothman's *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (Chapters 1-5 and Epilogue) and in Dennis Maloney's *Protection of Human Research Subjects*. Rothman details the abuses to which human subjects were exposed, culminating in Henry Beecher's 1966 article, "Ethics and Clinical Research," published in the *New England Journal of Medicine*, and ultimately

the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that Athe voluntary consent of the human subject is absolutely essential.≅ Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time.[2] The Code makes no provision for waiver or omission of consent.

In the United States, regulations protecting human subjects first became effective on May 30,1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status the National Institutes of Health (NIH) Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the

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contributing to the impetus for the first NIH and Food and Drug Administration regulations. Other equally useful sources include Robert J. Levine's *Ethics and Regulation of Clinical Research* (Chapter 14), Joan E. Sieber's *Planning Ethically Responsible Research*, Robert M. Veatch"s "Human Experimentation Committees: Professional or Representative?," and William J. Curran's "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies."

[2] Similar recommendations were made by the World Medical Association in *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, the 35th World Medical Assembly, Venice, Italy; the 41st World Medical Assembly, Hong Kong, 1989; and the 48th General Assembly, Somerset West, Republic of South Africa, 1996. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic research.

Institutional Review Board (IRB) as one mechanism through which human subjects would be protected.

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and suggested guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW.

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, which set forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles—respect for persons, beneficence, and justice—are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects. The *Belmont Report* also describes how these principles apply to the conduct of research. Specifically, the principle of respect for persons underlies the need to obtain informed consent; the principle of beneficence underlies the need to engage in a risk/benefit analysis and to minimize risks; and the

principle of justice requires that subjects be fairly selected.

In 1981, in response to the National Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the U.S. Food and Drug Administration (FDA) promulgated significant revisions of their human subjects regulations. The revisions did not alter the general principles of IRB review as they had evolved over the preceding three decades. Rather, they focused on the details of what the IRB is expected to accomplish and some of the procedures it must follow (Levine, 1986, p. 324).

These "basic" regulations became final January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule" as it is sometimes called) was promulgated by 16 federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted certain of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments. The Common Rule and other human subjects regulations are codified at Title 45 Part 46 of the Code of Federal Regulations, and it is the NIH Office for Protection from Research Risks (OPRR) that has taken the lead within the Federal Government on the task of harmonizing human subjects protections across agencies.[3]

[3] The Office for Protection from Research Risks (OPRR) fulfills responsibilities set forth in the Public Health Service Act. These include: (1) Developing and monitoring, as well as exercising compliance oversight relative to: (a) HHS Regulations for the protection of human subjects in research conducted or

When applied to research using stored human biological materials, a series of initial inquiries is needed to determine whether the regulations apply at all.

Is the research subject to federal regulation?

The federal regulatory protections only apply to: 1) research supported by funding from one of the federal agencies subscribing to the Common Rule; 2) research on an investigational new drug, device or biologic subject to FDA rules; or 3) research conducted at an institution that has executed an assurance with the Federal Government stating that even research not otherwise covered by the regulations will nonetheless be governed by them.

For example, an investigator performing privately funded research at a large university that has executed a "multiple project assurance" with the Federal Government almost always will

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supported by any component of the Department of Health and Human Services; and (b) PHS Policy on Humane Care and Use of Laboratory Animals involved in research conducted or supported by any component of the Public Health Service; (2) coordinating appropriate HHS regulations, policies, and procedures both within HHS and in coordination with other Departments and Agencies in the Federal Government; and establishing criteria for and negotiation of Assurances of Compliance with institutions engaged in HHS-conducted or supported research involving human subjects and those engaged in PHS-conducted or supported research using animals; (3) conducting programs of clarification and guidance for both the Federal and non-Federal sectors with respect to the involvement of humans and the use of animals in research; and directing the development and implementation of educational and instructional programs and generating educational resource materials; 4) evaluating the effectiveness of HHS policies and programs for the protection of human subjects and the humane care and use of laboratory animals; and (5) serving as liaison to Presidential, Departmental, Congressional, interagency, and non-governmental Commissions and Boards established to examine ethical issues in medicine and research and exercises leadership in identifying and addressing such ethical issues.

be required to abide by the federal regulations.[4] In addition, many multiple project assurance agreements include a provision that prevents researchers at that institution from evading federal regulation by conducting the research off-site or with a private, unregulated company. Instead, these multiple assurances typically promise that any researcher affiliated with the institution will abide by the federal regulations no matter where or with whom he or she works.

Thus, research on stored human biological materials carried out by a privately funded company, using only investigators who are free of affiliations with institutions that have executed a multiple project assurance, might not be subject to the federal human subjects regulations.

Does the activity constitute research?

The regulations do not apply to purely clinical interventions, even if they are experimental in nature. Rather, they apply to research, defined as "a systematic investigation designed to develop or contribute to generalizable knowledge." If the work on the stored materials is done solely as a clinical intervention, as might be the case in a pathology laboratory, then the federal regulations do not apply.

[4] The regulations require that each covered institution engaged in the conduct of research involving human subjects provide a written assurance of compliance, that it will comply with the requirements set forth in these regulations. The document is referred to as an "Assurance." Each Assurance sets forth the commitment of the institution to employ the basic ethical principles of the Belmont Report and to comply with the regulations. There are several kinds of Assurance documents. If an independent investigator is to

Work that has both a clinical and a research component, however, is covered by the federal regulations. Thus, a pathology laboratory that saves some tissue left over from a clinical intervention in order to do further, research-oriented testing would be subject to the federal regulations.

Does the research involve a "human subject"?

"Human subject" is defined by the regulations as "a living individual about whom an investigator conducting research obtains: (a) data through intervention or interaction with the individual, or (b) identifiable private information."

From this definition it is apparent that an investigator who interacts with a person in order to obtain a new blood or saliva sample is doing human subjects research, regardless of whether the investigator records any personal information about the subject.

When working with existing stores of biological materials, an investigator is defined as doing research on a "human subject" when he or she obtains "identifiable private information." Section 46.102(f)(2) defines "identifiable" to mean the identity of the subject is or may readily be ….associated with the information. OPRR interprets "identifiable" to include specimens with codes that, with the cooperation of others, could be broken open in order to reveal the name of

provide an assurance of compliance to OPRR the document is called an Agreement.

the tissue source.[5] Thus, research on specimens that have no personal identifiers and no codes linked to personal identifiers would not be covered by the regulations because no human subject would be involved.

On the other hand, research on specimens that are linked, even through a code, to personal information about the tissue source constitutes research on a human subject and is subject to the federal regulations.

For example, imagine a researcher interested in doing basic work toward the development of the mapping and sequencing of the human genome. He or she might request tissue samples from a repository that has stored samples from an entire kin group. The samples are identified by position within the kin group (e.g., "father", "daughter," "maternal aunt"), but the identity of the family was never recorded at the time the samples were collected. Thus, even if the investigator and the repository were to attempt to recontact the tissue donors, it would be impossible, because their identities are entirely unknown and unknowable. In this scenario, there would be no human subject of research involved; no IRB review would be necessary, nor would consent from the tissue donors for new and unanticipated forms of research be required.

IRB REVIEW REQUIREMENTS FOR RESEARCH SUBJECT TO THE FEDERAL REGULATIONS

[5] Personal communication from Dr. Gary B. Ellis, Director, OPRR, April 8, 1998.

For situations in which biological material donors are identifiable and, therefore, the federal regulations apply, two basic protections for human subjects generally come into play. First, IRB review is required to ensure an acceptable balance between risks and benefits, and second, subject enrollment is permitted on the condition that informed consent is properly obtained. There are, however, exceptions and variations that are pertinent to research on human biological materials.

First, the twin protections of consent and IRB review do not apply if the research is found to be exempt from the federal regulations. The person given the authority to determine if an exemption applies will vary among institutions, depending upon the assurance they negotiated with the government. In many cases, that person will be the chair of the research or clinical department in which the investigator works. In others, it will be the chair or the administrator of the IRB.

The regulations state that such an exemption may be applied to "research involving the collection or study of existing. .specimens. . .if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects."

Currently, OPRR interprets this regulation to mean that investigators who conduct

research with coded samples are not eligible for the exemption, if there is any way to links particular results to particular samples, are not eligible for a waiver if there is any means by which the codes could be broken (including by cooperation with other people and institutions) and specific research results linked to specific subjects.

On the other hand, if a coding system were developed that used encryption schemes to permit updated clinical information to flow downstream to the investigator using the specimen, but that absolutely precluded the possibility of linking a specimen upstream back to the source (including by cooperation with other people and institutions), this research would be eligible for an exemption from the requirements for subject consent and IRB review.

Expedited IRB Review

For research that is not exempt from IRB review and subject consent, there are nonetheless opportunities for streamlining the review process and obviating the need for consent.

First, an IRB may use expedited review procedures when a protocol involves no more than minimal risk [46.110]. In short, the IRB chair or one or more experienced reviewers, designated by the chair from among members of the IRB, review the research and approve it or refer it to the IRB for full IRB discussion. To qualify for expedited review, an activity must: (1)

involve no more than minimal risk and be found on the list published at Federal Register 46: 8392; Jan. 26, 1981;[6] or (2) be a minor change in previously approved research during the period of 1 year or less for which approval is authorized by the IRB.

For research on human biological materials, a key question concerning eligibility for expedited review will be whether the research poses more than a minimal risk to the subject. This assessment will depend upon the kind of information being sought in the specimen, its psychosocial and clinical significance for the subject, and the likelihood that the finding will be transmitted to the subject, or to anyone else who could associate the findings with the subject.

Revealing Interim Findings and Concepts of Risk

Experts disagree about whether interim or inconclusive findings should be communicated to subjects, although most agree that they should not because only confirmed, reliable findings

[6] This list, which is currently being revised, includes: 1) collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth; if patient care indicates a need for extraction; 2) collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor; 3) recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practices; 4) collection of blood samples by venipuncture, in amounts not exceeding 450 ml in an 8-week period and no more often than 2 times per week, from subjects 18 years of age or older and who are in good health and not pregnant; 5) collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted techniques; 6) voice recordings made for research purposes; 7) moderate exercise by healthy volunteers; 8) the study of existing data, documents, records, pathological specimens, or diagnostic specimens; 9) research on individual or group behavior or characteristics of individuals; 10) research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required (46 FR 8392; January 26, 1981).

constitute "information." Persons who oppose revealing interim findings argue that the harms that could result from revealing preliminary data whose interpretation changes when more precise or reliable data become available are serious, including anxiety or irrational (and possibly harmful) medical interventions. They argue that such harms are avoidable by controlling the flow of information to subjects and limiting communications to those that constitute reliable information.

MacKay (1984), writing about the development of genetic tests, argues against revealing interim findings, contending that preliminary results do not yet constitute "information" since "until an initial finding is confirmed, there is no reliable information" to communicate to subjects, and that "even...confirmed findings may have some unforseen limitations" [p. 3]. He argues that subjects should not be given information about their individual test results until the findings have been confirmed through the "development of a reliable, accurate, safe and valid presymptomatic test" [pp. 2-3; see also Fost and Farrell (1990)]. Others have argued that all interim results should be shared with subjects, based on the principle of autonomy, that subjects have a right to know what has been learned about them.

Reilly (1980) suggests that IRBs develop general policies governing the disclosure of information to subjects, to help make these determinations. He suggests that at least the following three factors be considered: "1) the magnitude of the threat posed to the subject; 2) the accuracy with which the data predict that the threat will be realized; and 3) the possibility that

action can be taken to avoid or ameliorate the potential injury" [p. 5]. IRBs should ask investigators to define three categories of disclosure: 1) "findings that are of such potential importance to the subject that they must be disclosed immediately;" 2) "data that are of importance to subjects..., but about which [the investigator] should exercise judgment about the decision to disclose....[i]n effect, these are data that trigger a duty to consider the question of disclosure;" and 3) "data that do not require special disclosure" [pp. 5, 12].

IRBs should consider whether the investigator's approach appropriately balances the risks and benefits involved in providing access to the data. Subjects should be told, as part of the consent process, whether, when, and what information they will receive. Any disclosures of genetic information should be accompanied by appropriate counseling by trained genetic counselors. However the IRB resolves this question, investigators should explain to prospective subjects the basis according to which they will decide which data will be disclosed to whom, and when those disclosures will be made.[7]

[7] Another important issue is that subjects generally retain the right not to receive information about the results of a study that reveals their genetic status. A possible exception involves circumstances where early treatment of genetically linked disease could improve the subject's prognosis. In such circumstances, investigators may have a duty to inform the subject about the existence of the genetic defect and to advise him or her to seek medical advice. [See, e.g., Andrews (1991).] (As of this writing, a legal duty of investigators to inform subjects about the existence of genetic defects has not been firmly established.)

IRBs should also ensure that investigators adequately deal with how they will handle incidental findings; that is, what will be done with genetic information that is learned during the course of the study that does not directly relate to the research. For example, in intergenerational pedigree analyses, questions of paternity or parentage can come up. DNA analysis will reveal information indicating that an individual's biological parents are not who he or she thought they were; blood typing may reveal similar information. DNA analysis may also reveal information about diseases or conditions other than the disease or condition under study. Prospective subjects should be informed during the consent process that the discovery of such

CONSENT REQUIREMENTS

Regardless of whether a protocol using human biological materials is eligible for expedited review or requires standard review by the IRB, the requirement for donor consent may be subject to discussion. While the presumption for all human subjects research is that consent is required, this requirement can be altered or waived if certain criteria, set forth at 45 C.F.R. Sec. 46.116(d), are met:

1) the research involves no more than minimal risk to the subjects;
2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3) the research could not be practicably carried out without the waiver or alteration; and
4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

For research with human biological materials, then, a request to waive consent by the original donor could be granted by an IRB if it could be shown that: 1) the research neither affects the rights of subject nor poses more than a minimal risk of psychosocial harm (including distress at receiving genetic information, stigmatization or discrimination if third parties become privy to

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information is possible. Appropriate counseling should be provided to educate subjects about the meaning of the genetic information they have received, and to assist them in coping with any psychosocial effects of participation.

the information etc); 2) it is impossible or extremely difficult to contact the tissue donors to obtain consent; and 3) a plan is made to provide information to subjects after the fact, where appropriate.

APPLYING THE REGULATIONS TO A TYPICAL PROTOCOL

Imagine a hypothetical gene for a form of prostate cancer. Researchers might wish to screen large numbers of samples of prostate tissue currently stored in academic and commercial repositories, in order to identify those with markers for the gene. Having identified this subset, investigators would then wish to examine the medical records of those men who appear to have the gene, in order to correlate such things as medical history, symptomology, characteristics of the tumor, treatment choices, and outcomes. This work, in turn, might yield further subsets worthy of more refined study, as researchers attempt to correlate the gene with a particular type of tumor or response to treatment.

Under current regulations, any link between the specimens used by the researcher and the men from whom the materials were obtained would qualify the research as "human subjects research." This identifiability, even if mediated by coding systems, would trigger the requirement for IRB review. Absent encryption schemes that allow only unidirectional flow of information, IRB review could not be waived. The review might be eligible for expedited procedures, however, if it were deemed to be of minimal risk to the subjects and is listed on the Federal

Register notice that identifies the kinds of research eligible for expedited review (See Tables x and y).

The initial screen of all samples, done solely for the purpose of identifying which men have the gene might qualify as minimal risk, depending on the likelihood that any finding would be communicated to the individual tissue donors and whether such communications pose the risk of significant psychosocial distress.

On the second screen, in which the subset of men whose tissues show a marker for the gene will now have their medical records examined, the same issues about minimal risk apply, but with a seemingly greater risk that findings will develop in the course of research that might tempt investigators to consider communicating their finding to the tissue donors or their physicians. For example, if the data strongly indicate that those with the markers respond dramatically better to one treatment than another, investigators may wonder whether it would be best to communicate this information to patients and their physicians so that the better treatment can be pursued before the patient's health irreversibly declines.

At the same time, the tentative nature of these findings may make their communication problematic. Since some prostate treatments often have significant side-effects, such as impotence, and since the clinical data on the need to detect and treat slow-growing prostate

cancers is mixed, such tentative findings may put patients into a position of great uncertainty and anxiety, without the assurance of clinical benefit.

It is the difficulty of understanding the meaning of "minimal risk" with regard to psychosocial harm (as opposed to physical harm) that makes this issue so complex, and, in turn, makes the decision about eligibility for expedited review so uncertain.

Psychological risk includes the risk of harm from learning genetic information about oneself (e.g., that one is affected by a genetic disorder that has not yet manifested itself). Complicating the communication of genetic information is that often the information is limited to probabilities. Furthermore, the development of genetic data carries with it a margin of error; some information communicated to subjects will, in the end, prove to be wrong. In either event, participants are subjected to the stress of receiving such information. For example, researchers involved in developing presymptomatic tests for Huntington Disease have been concerned that the emotional impact of learning the results may lead some subjects to attempt suicide. They have therefore asked whether prospective participants should be screened for emotional stability prior to acceptance into a research protocol.

Note that these same disclosures of information can also be beneficial. One of the primary benefits of participation in genetic research is that the receipt of genetic information, however

imperfect, can reduce uncertainty about whether participants will likely develop a disease that runs in their family (and possibly whether they have passed the gene along to their children). Where subjects learn that they will likely develop or pass along the disease, they might better plan for the future. To minimize the psychological harms presented by pedigree research, IRBs should make sure that investigators will provide for adequate counseling to subjects on the meaning of any genetic information they might receive. Genetic counseling is not a simple matter and must be done by persons qualified and experienced in communicating the meaning of genetic information to persons participating in genetic research or persons who seek genetic testing.

Social risks include stigmatization, discrimination, labeling, and potential loss of or difficulty in obtaining employment or insurance.[8] Changes in familial relationships are also social ramifications of genetic research.

Regardless of whether expedited review is permitted by the local IRB or standard review is required, the IRB may then consider whether subject consent to do the research can be waived.

[8] For example, an employer who knew that an employee had an 80 percent chance of developing HD in her 40s might deny her promotion opportunities on the calculation that their investment in training would be better spent on someone without this known likelihood. Of course, the company may be acting irrationally (the other candidate might be hit by a car the next day, or have some totally unknown predisposition to debilitating disease), but the risk for our subject of developing HD is real, nonetheless. One problem with allowing third-parties access to genetic information is the likelihood that information, poorly understood, will be misused. Likewise, an insurer with access to genetic information may be likely to deny coverage to applicants when risk of disease is in an unfavorable balance. Insuring against uncertain risks is what insurance companies do; when the likelihood of disease becomes more certain, they may refuse to accept the applicant's "bet."

Once again, the question of minimal risk must be answered. In addition, the investigators would need to show that doing the research without subject consent is necessary because it is impractical to contact the donors, and that doing the research without consent will not affect the rights of the subjects.

Given the subtlety of these inquiries, it would not be surprising to find that IRBs have different rulings. Some, for example, might find that the initial screening to identify the subset of samples with markers for the gene ought to be eligible for expedited review and a waiver of consent, but that subsequent work on the subset ought to require full review and subject consent. Others might waive consent for all aspects of the research, and still others for none.

This variability in IRB response is relevant, because many protocols will involve repositories at one institution, and investigators at one or more different institutions. Since the regulations require that each institution's own IRB conduct its own review, the repository and the investigators may find that they are being held to different rules about the need to obtain consent. This phenomenon, a common occurrence in collaborative research of all types, has drawn criticism from the research community, as it adds to the time and complexity of getting all necessary approvals. For example, a researcher at Institution A, which has decided that consent is required for all stages of the work, might be precluded from collaborating with an investigator from Institution B, where consent requirements were waived. The decision about whether to

permit the collaboration will lie in the hands of Institution A's IRB.

The justification for multiple IRB reviews lies in part in the philosophy of local review to reflect local standards of human subjects protections, and in part on the expectation that IRBs are fallible, and that multiple reviews minimizes the possibility of a serious error due to the incorrect ruling by one particular IRB.

PROFESSIONAL STANDARDS

When NBAC began its review of the use of human biological materials in research, it was aware that a number of scientific and medical organizations had done thoughtful work on the issue. The work of a number of these organizations lead to the development of position statements and recommendations that reflected their efforts to work through the many ethical and policy issues the topic raises. To provide NBAC with an understanding of the range of positions that exist among organizations which have carefully considered this subject, NBAC conducted a comparative analysis of these statements as they applied to the issue of protections for the appropriate use of human biological materials in research.[9] In particular, this analysis assisted the Commission in understanding how its recommendations might compare to those of other groups. The comparison was not initiated to assess or evaluate the strengths or weaknesses of any

[9] Fourteen statements, published and widely discussed in the literature, or available on the World Wide Web, were reviewed. They are listed separately in Appendix D.

statement.

Definitions: What Constitutes "Identifiable" Information?

The concept of anonymity is one source of complexity in discussing appropriate use of human biological materials. As discussed earlier in this chapter, current human subjects regulations only distinguish between information that either does or does not allow identification of an individual. But as professional groups consider what constitutes information sufficient to identify an individual, some have constructed a number of categories that define degrees of biological material identifiability. Consequently, when groups discuss "identifiable" samples they may mean different things.

A source of consistency that aided comparison of statements, was that all organizations categorized materials using the same method: the degree to which the samples as stored are able to be identified as coming from a particular individual.[10] Nonetheless, different terms describing categories of materials are used across statements and, where the same terms are used, they are not defined in the same manner.

Although different terms were applied to label the categories, four categories describing levels of identifiability of human biological materials were discussed in these statements. For the

[10] No statements provide explicit justification for this method of categorization.

purpose of the comparative analysis, the terms describing categories of human biological materials were adapted from two of the sources to yield the following:[11] **Anonymous** biological materials were originally collected without identifiers and are impossible to link to their sources; **Identifiable** biological materials are either directly identified or coded, such that a subject can be identified either directly or through decoding; such materials are not now or will not be made anonymous; **Coded** biological materials are unidentified for research purposes, but can be linked to their sources through the use of a code; **Directly identified** biological materials are those to which identifiers, such as a name, patient number, or clear pedigree location, are attached and made available to researchers.

An example of the difficulties that arise when terms are not defined or applied uniformly in the course of a comparison is demonstrated in a recent article by Lori Andrews and Dorothy Nelkin. The authors write:

> Because of the risks of research-uses of even *anonymised tissue,* the American Society of Human Genetics and the American College of Medical Genetics recommend that individuals be asked whether or not they wish to allow its *anonymous use* before tissue is taken from them (emphasis added.) (Andrews, 1998)

[11] These definitions are adapted from those discussed by the American Society of Human Genetics, AStatement on Informed Consent for Genetic Research,≅ 1996; and Clayton, E.W., Steinberg, K.K., Khoury, M.J., Thomson, E., Andrews, L., Kahn, M.J.E., Kopelman, L.M., and J.O. Weiss, AInformed Consent for Genetic Research on Stored Tissue Samples,≅ *JAMA* 274:1786-1792, 1995.

The American Society of Human Genetics (ASHG) does not use the classification "anonymous use" in its recommendations (ASHG, 1996). It does, however, discuss the appropriate use of anonymous or anonymized materials stating, "[obtaining consent] should be encouraged, except for the prospective studies in which samples are collected anonymously, or have been 'anonymized'". This position seems to contrast with the position Andrews and Nelkin describe. However, if Andrews and Nelkin are using the phrase "anonymous use" to apply to "identifiable" samples (a term that is used in the ASHG statement) that are coded and could be said to be used in an anonymous manner in the research, then their interpretation of the statement seems accurate. Nonetheless, there is no textual or contextual evidence in the ASHG statement to support the imposition of a system of classification based on how the tissues are *used* in research. In other words, there is no justification for applying the category "anonymous use" to "identifiable" samples.

This example highlights the importance of definitions in crafting guidance on a subject. In particular, how does one avoid ambiguities of interpretation when discussing "identifiable" materials?

Protections: Recommended Human Subjects Protections

Many groups recommend different protections according to the degree to which samples

used in a research protocol can be identified with a subject. Therefore, how a group defines what constitutes identifiable information often influences what protections it recommends. Having identified and defined the categories of materials that would be used in comparing the statements, NBAC examined what protections the statements recommended for permissible use of existing, and permissible future collection and use of human biological materials. This was done primarily to gain an understanding of what the organizations discussed in terms of the appropriate level of protection for research using human biological materials. As well as providing NBAC with an understanding of the range of protections discussed, the comparison also revealed some innovative ideas for protections that have been discussed by several organizations.

The statements varied in precision and comprehensiveness: Not all of the statements explicitly distinguish between categories of sample identifiability; those that do distinguish do not necessarily address the issue of protections according to each category; and some statements do not explicitly address protections for permissible use of existing materials, but instead provide principles for applying protections when materials are collected in the future. Overall, there was more discussion regarding protections for future collection than for the use of existing materials.

Two protections that appear throughout most of the statements, although they are not applied uniformly, are informed consent and institutional review board (IRB) review. Some statements provide guiding principles or factors to consider when making decisions about the

appropriate use of materials in research. Others explicitly recommend the application of these protections to categories of human biological materials.

For those statements that use the latter approach, an obvious source of variation in recommending the application of protections is different understandings of whether coded samples should be considered identifiable. Some statements use "identifiable" to mean exclusively "coded" materials; others use "identifiable" to encompass both "coded" and "directly identified" materials. Statements developed by ASHG and the National Institutes of Health/Centers for Disease Control and Prevention (NIH/CDC) Workshop (Clayton, 1995) illustrate these two usages of "identifiable."

ASHG provides a table indicating "[s]uggested guidelines on the need to obtain informed consent in genetic research, by type of study design and level of anonymity." (ASHG, 1996) In this format, the statement indicates explicitly whether informed consent should be required for each category of human biological materials. Although ASHG differentiates between "identifiable" (meaning coded) and "identified" (meaning directly identified) samples, it recommends the same protections for both.

The NIH/CDC Workshop does not differentiate between coded or directly identified samples when applying protections. According to the Workshop participants, AEven if the

researcher cannot identify the source of tissue, the samples are not anonymous if some other individual or institution has this ability" (Clayton, 1995). Accordingly, they propose, "All research that proposes to use samples that are not now or will not be made anonymous requires more thorough review."

Thus, when recommending IRB review and informed consent, coded and directly identified materials are treated as requiring equal levels of protection.

The Pathologists Consensus Statement recommends that different protections be applied to research using archived coded than to research using directly identified samples. The statement emphasizes the importance and feasibility of, "maintaining patient identity and clinical information separate from research data through the use of coding" (Pathologists, 1997). In this way, they reason, the research use of coded materials does not pose the same risks to subjects as the use of directly identified materials, and does not require the same protections. Instead, the statement proposes the following:

> When information about the specimen source is withheld from researchers and any link is provided only through IRB-approved confidentiality procedures, the risk to research subjects from unauthorized breach of confidentiality is minimal. We therefore recommend that where institutions and IRBs approve confidentiality policies and regard them as

providing sufficient protections for patients from improper disclosure of information in the medical record, such approval should be regarded as adequate evidence of the ability to secure medical record information for research applications.

The Ethics Committee of the Human Genome Organisation (HUGO) is unique in placing primacy in its recommendations concerning the use of stored materials in research on the following two factors: (1) "the source of the sample, that is, whether it was collected during routine medical care or during a specific research protocol . . ."; and (2) whether there was, at the time the sample was collected, "general notification" of the institution's policy concerning future uses of samples. Of the categories of materials it defines, the HUGO Ethics Committee recommends the most stringent protection for the research use of "routine samples, obtained during medical care and stored . . . before notification of such a policy" (HUGO, 1998). Such samples may only be used if, provided there is ethical review, they have been anonymized prior to use. All other samples may be used if, again provided there is ethical review, the patient or participant "has not yet objected, and the sample to be used by the researcher has been coded or anonymized."

Instead of explicitly recommending protections, some statements provide guidelines for making decisions about appropriate use of stored materials. These decisions include the following: (1) when and how to recontact individuals regarding consent for new research uses of

their samples; (2) how to judge the adequacy of previously given consent; and (3) how to assess protocols that propose to remove identifying information from samples before using them in research.

The statement from the American College of Medical Genetics (ACMG, 1995) lists factors to be considered "in deciding whether it is appropriate to use previously collected samples without contacting the individual": "[A]re or will the samples be made anonymous?; the degree to which the burden of contacting individuals may make it impracticable to conduct research; existence and content of prior consent; and risks and benefits."

When it is determined that it would be inappropriate to use samples without contacting individuals, the statement also provides guidance regarding how to recontact individuals: "Contacts regarding new research should address its purpose, limitations and possible outcomes, methods for communicating and maintaining confidentiality of results, duration of storage, uses of samples or results in studying others (anonymously), and sharing samples with other researchers for other types of research" (ACMG, 1995).

The NIH/CDC Workshop statement, addressing the use of existing identifiable samples, lists five factors for IRBs to consider "in deciding how to assess protocols that propose to make existing identifiable samples anonymous for use in research" (1791):

(1) whether the information the researcher seeks can be obtained in a manner that allows individuals to consent (this includes the possibility of using tissue samples for which people had previously given permission for use in research); (2) whether the proposed investigation is scientifically sound and fulfills important needs; (3) how difficult it would be to recontact subjects (it is not necessary, however, to prove impracticability); (4) whether the samples are finite and, if used for research, they may no longer be available for the clinical care of the source or his or her family (for example, use of tumor samples may be more problematic than use of transformed permanent cell lines); and (5) how the availability of effective medical interventions affects the appropriateness of pursuing anonymous research (Clayton, 1995).

A statement developed by the National Heart, Lung, and Blood Institute (NHLBI, 1997) also addresses the appropriate use of existing samples by providing guidelines for decision-making rather than advocating specific protections. It lists several issues for IRBs and funding agencies to consider "[i]n judging the adequacy of a previous informed consent when an application is received to do new genetic research": "(1) the nature of the disease proposed for study, (2) the likelihood that knowing results of the research will harm or benefit an individual, (3) the availability of effective treatment or prevention for the disorder, and (4) the burden of such treatment."

Recommended protections for future collection of human biological materials varied among the statements. For example, the statements give different emphasis on informed consent. The types of consent proposed ranged from general consent (consent to future, unspecified research uses of the material), to layered consent (offers the subject the option to consent to a variety of classes of research), to specific consent for a unique designated protocol.

In some cases the statements offer insightful discussion regarding what level of consent is appropriate for the use of materials. Regarding general consent, ASHG points out that in certain instances general consent may be inappropriate, noting that "[i]t is inappropriate to ask a subject to grant blanket consent for all future unspecified genetic research projects on any disease or in any area if the samples are identifiable in those subsequent studies." On the other hand, the Pathologists Consensus Statement notes that there may be value in requiring general consent stating, "[t]o give a description of each and every research protocol which might be performed in the (sometimes distant) future on a patient's tissue is an unreasonable burden for the patient and the researcher" (Pathologists, 1997).

Several statements advocate a form of layered consent for collecting all samples in the future. NHLBI provides thoughtful discussion on the content of a proposed three-tiered consent. In such a consent, as NHLBI describes, one is offered the option of consenting to the current

study (first level), a study with goals broadly related to the area of the original study (second level), and a study with goals unrelated to the area of the original study (third level). (NHLBI, 1997).

Highlighting the importance of designing adequate informed consent mechanisms in the future, the PRIM&R/ARENA Tissue Banking Working Group[12] statement is unique among the analyzed statements in focusing primarily on future collection and use: "The Working Group believes that when organizations with access to specimens act according to the following criteria, it should generally be unnecessary to obtain further consent from patients." The group acknowledges that its principles apply to "prospective specimen collection," and does not make explicit recommendations for the use of existing samples. However, these carefully developed principles can be adapted "to allow . . . pathologists to make their collections available for research and, at the same time, protect the privacy and confidentiality of the tissue sources."

In addition to IRB review and informed consent, some organizations discussed ideas for other protections. NHLBI outlines a proposal for an advisory board to manage the use of stored materials:

NHLBI should establish a facilitator function for the valuable resource of stored

[12] *Model Consent Forms and Related Information on Tissue Banking from Routine Biopsies*, Compiled by the National Action Plan on Breast Cancer Tissue Banking Working Group, with comments by the PRIM&R/ARENA Tissue Banking Working Group, 1997.

specimens. Similar to other valuable collections, the facilitator will maintain organization and control access to utilization. The facilitator function should be carried out by an Advisory Board, including some of the original investigators who collected the specimens, genetic researchers similar to those who will request specimens, and the public. Specifically, this NHLBI Advisory Board must attend to informed consent issues, carefully reading previous consent documents and considering their applicability to current requests, based on the guidelines set forth above. To enhance public accountability, the Advisory Board and investigator(s) should seek advice about consent issues from members of the group whose tissues will be studied (NHLBI, 1997).

Some statements recommend that institutions that store and/or distribute human biological materials have in place IRB-approved policies for protecting confidentiality. Groups such as those endorsing the Pathologists Consensus Statement, reason that these policies are an important element in any policy governing the research use of human biological materials, that seeks to protect human subjects.

Statements that discuss institutional confidentiality policies tend to emphasize the importance of permitting investigators access to updated clinical information associated with human biological materials. The Association of American Medical Colleges (AAMC) describes the importance of maintaining access to such information:

> A great deal of contemporary research is dependent on the ready accessibility of personally identifiable, i.e., linkable, archival patient materials, such as medical records and tissue specimens removed in the course of routine medical care. . . .As a rule, these kinds of studies [epidemiologic and health services research] do not require that the identity of the patient be known to the investigator. But in the great majority, the investigators must have the ability to obtain additional, or follow up information about particular sets of subjects in order to evaluate the significance of the findings and interpret them in an appropriate biological, clinical or epidemiological context. The only way such additional information can be gathered in studies of archival patient materials is if the materials are coded in such a way that they remain permanently linkable to specific patients (AAMC, 1997).

The AAMC also proposes one way that secured access to such information could be maintained:

> One possible approach to this task would be to give each patient at his/her first encounter with the health care system two unique identifiers, one for clinical use, the other for research. Both numbers would be permanently associated with the specific individual. The linkage between the two numbers would be securely maintained in a protected

location with controlled access . . . . (AAMC, 1997).

Statements that emphasize the importance of institutional confidentiality mechanisms are less likely to recommend protection in the form of IRB review and informed consent. They are more likely, however, to contribute to a discussion of confidentiality mechanisms. With such mechanisms in place, the Pathologists Consensus Statement reasons, IRBs should be permitted "broader latitude to waive the requirements for informed consent for research on identifiable (linkable or coded) samples" (Pathologists, 1997).

In sum, all statements used a similar method of categorizing research on human biological materials, a method based on the degree of identifiability of the materials as stored. The statements varied in the way they defined the categories of anonymity of samples and the protections recommended for each category. Finally, these statements contained some but not explicit discussion about the mechanisms for ensuring the materials are stored and/or used in such a way that the confidentiality of the source of the material is promoted.

INTERNATIONAL GUIDELINES

[To be written]

A number of other countries has addressed this issue through bodies similar to NBAC

They have identified similar issues.

Local rules may differ.

CONCLUSIONS

The National Bioethics Advisory Commission has the opportunity to develop a wholly new approach to research with human biological materials or to work within the existing structure to clarify or change specific aspects of the regulations.

Among the items appropriate for Commission attention are:

- Should the use of coded samples continue to be regarded as research on human subjects? If it should, no change in the regulatory language or interpretations is needed. If not, new regulatory language will need to be adopted.

- What should qualify as a violation of donor's rights? What is the current state and federal law governing ownership of these materials and does their use without consent violate that law? What is the current state and federal law governing use of medical records, and how does

their use in conjunction with research on these samples affect the rights of the donors? In light of these analyses, should interpretive guidance be offered by the Commission?

- What constitutes minimal risk where risks are psychosocial in nature? How does one incorporate into this analysis the aspects of protocol design that are intended to slow or prevent the flow of intermediate (or even final) findings back to the tissue donors and their treating physicians? In light of these analyses, should interpretive guidance be offered by the Commission?

- What must a researcher show in order to demonstrate that the research could not practicably be carried out without a waiver of consent? Is expense a legitimate part of that showing, or is it the obligation of researchers to seek funding adequate to accommodate the costs of contact? If funding should include an effort to contact, how much effort must be expended? Is it enough to make one call or mailing to the last known address, or must researchers make some effort to track down donors who have moved? In light of these analyses, should interpretive guidance be offered by the Commission?

- With collaborative research the norm in this area, if only because there will frequently be at least two institutions—the investigator's and the repository involved—should the rules requiring independent review by each institution's IRB be amended?

- Overall, then, research on stored human biological materials will be subject to federal regulations for IRB review and informed consent except when done by uncovered investigators at uncovered institutions, or when done with samples for which there is no possible way to track back to the original donor. Research subject to IRB review, however, may be eligible for expedited review and an easing or elimination of consent requirements, if the research poses no more than a minimal risk to subjects and otherwise meets various criteria. Significant ambiguities exist in the current regulations with regard to criteria crucial to triggering expedited review or a waiver of consent, and significant policy choices could be made with regard to the definition of human subject and the need for multiple IRB reviews. It is on these topics that the Commission could choose to focus its attention.

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