March 18, 1998: This is a draft paper developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced.

IV. COMPARATIVE ANALYSIS OF PROFESSIONAL ORGANIZATION STATEMENTS AND RECOMMENDATIONS AND EXISTING FEDERAL REGULATIONS REGARDING THE COLLECTION AND USE OF HUMAN BIOLOGICAL MATERIALS

When NBAC began its review of the use of human biological materials in research, it was aware of a number of position statements and recommendations already developed by various scientific and medical organizations that addressed the issue. 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. The purpose was twofold: 1) to understand how these documents compared, particularly with respect to the categories of research they describe and the human subjects protections they recommend; and 2) to examine and illustrate how NBAC's conception of the issues compared with those of existing statements.

PROFESSIONAL ORGANIZATIONS

Twelve statements, published and widely discussed in the literature, or available on the World Wide Web, were reviewed. These statements represent the views of a range of professional and scientific organizations. The comparison was conducted to provide NBAC with an understanding of the range of positions that exist among organizations who have thoughtfully and carefully considered this subject. In particular, this analysis assisted NBAC in understanding how its recommendations compared to those of other groups. The comparison was not initiated to assess or evaluate the strengths or weaknesses of any statement.

Definitions: Categories of Human Biological Material

Terminology is one source of complexity in discussing appropriate use of human biological materials. To carry out a comparison of a number of statements authored by different organizations, NBAC faced the challenge of accommodating the various categories of human biological materials discussed across all of the statements. A source of consistency that aided the comparison 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[1]. Nonetheless, different terms describing the categories of materials are used across statements and, where the same terms are used, they are not defined in the same manner.

Four categories describing levels of identifiability of human biological materials were discussed in these statements, although different terms were applied to label the categories. For the purpose of the comparative analysis, the terms describing categories of human biological materials were adapted from two of the sources to yield the following:[2] **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.[3] (emphasis added.)

The American Society of Human Genetics (ASHG) does not use the classification "anonymous use" in its recommendations. 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'"[4]. This position seems to contrast with the position Andrews and Nelkin described. However, if they are using the phrase "anonymous use" to apply to "identifiable" samples (a term that is used in the ASHG statement) that are used in an anonymous manner in 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 classification framework 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 the term "identifiable" is applied inconsistently across several statements? Some statements use "identifiable" to categorize exclusively "coded" materials; others use "identifiable" to categorize 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[5] illustrate these two usages of "identifiable." The definition of "identifiable" employed in NBAC's comparative framework accurately captures statements that use either definition.

Protections: Recommended Human Subjects Protections

The definitions of categories of human biological materials become particularly significant when protections are applied based on these categories. Having identified and defined the categories that would be used in the comparison, 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. The comparison also provided NBAC with an understanding of the range of protections, including some innovative ideas for protections, that have been discussed by several organizations.

NBAC found that 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 for the collection of future material.

Overall there was more discussion regarding protections for future collection than for use of existing materials. All of the statements discuss, in varying degree of detail, the protections that ought to be in place for future collection and use of human biological materials; not all of them, however, explicitly discuss protections for existing samples.

The PRIM&R/ARENA Tissue Banking Working Group[6] statement is representative of those statements exhibiting a forward-looking approach, 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" (p. 1/5) 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" (p. 3/5).

Addressing the use of previously collected human biological materials in research, some statements, instead of recommending specific protections, provide guidelines for making decisions about appropriate use. The statement from the American College of Medical Genetics[7] (ACMG) addresses the use of existing samples broadly, listing 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." The statement also provides guidance regarding recontacting 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."

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.[8]

The statement developed by the National Heart, Lung, and Blood Institute[9] (NHLBI) 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."[10]

In a few cases, statements recommend specific protections for the appropriate use of existing samples. A clear example of this approach can be found in the statement developed by ASHG. 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." In this format, the statement indicates explicitly whether informed consent should be required for each category of human biological 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. An obvious source of variation in the application of these two forms of protection is found in the category of existing materials that are identifiable. In part, this variation can be attributed to the different definitions of "identifiable" samples, discussed above. Some statements do not explicitly subdivide the category "identifiable" into "coded" and "directly identified", and therefore *de facto* apply the same protections to the two categories, as demonstrated in the statement developed by the NIH/CDC Workshop. Further, several statements that do explicitly discuss the two subcategories apply the same, as in the ASHG statement, or different levels of protections, as in the Pathologists Consensus Statement, to both.

The statements also reflect a variety of positions regarding recommended protections for future collection of human biological materials. Most of this variation centers on the issue of informed consent: whether it should be required, and if so what ought to be its nature. 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." 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" (6).[11]

Several statements advocate a form of layered consent for collecting all future samples. NHLBI provides thoughtful discussion on the content of a proposed three-tiered consent. In such a consent, 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).[12]

In addition to IRB review and informed consent, the 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 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 (15-16)[13].

Some statements recommend that institutions that store and/or distribute human biological materials have in place IRB-approved policies for protecting confidentiality. The Pathologists

Consensus Statement contains a description of the content of such a policy:

> All pathology departments should have a written policy concerning confidentiality and privacy rights. The policy should include specific procedures for access to the medical record; confirmation of approval of research involving the use of human tissues by an institutional review board where appropriate . . . ; a description of safeguards to prevent unauthorized access; procedures for the release of information; methods of ensuring that everyone with access or who might gain legitimate access embrace the need for privacy, confidentiality and security of patient information; specific procedures for records kept in electronic form; and specific procedures for the release of information for research" (2).[14]

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."[15]

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 . . . .[16]

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":

> Breach of confidentiality is the major risk research subjects encounter when it is possible to link a specimen to a source. 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 be regarded as adequate evidence of the ability to secure medical record information for research applications."[17]

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.

FEDERAL REGULATIONS

Federal rules regulate scientific research involving human biological material. By its own terms, 45 C.F.R. § 46.101 "applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research." In practice, the "Common Rule," as the regulations have become known, applies to the (currently) seventeen federal agencies and departments that have adopted its constraints.

There are narrow exceptions to the Common Rule, listed in 45 C.F.R. § 46.101(b). For the purposes of this chapter, the exception listed in section (b)(4) is particularly relevant:

> (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or 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.

According to this language, anonymous research on existing samples of human biological material is excepted from, and therefore not subject to, the requirements of Part 46, which include such processes as IRB review and informed consent.

Interpretation of the regulations' application to all other scenarios of research involving human biological material is more difficult. First, section (b)(4) explicitly refers to "existing" pathological or diagnostic specimens, presenting at the outset the issue of defining the term. Should "existing" indicate specimens stored as of a particular (perhaps regulatory) date, or could the term follow a more flexible approach, applying to any stored specimen at the point the researcher commences her project? Would the more flexible approach circumvent the regulatory purpose of a uniform approach to all prospective research? The regulations themselves provide no benchmark by which to measure "existing" and remedy this confusion.

This issue can be illustrated as follows: Where T_0 = the date of effectiveness of the regulations, T_1 = a future date, and $T_{(-1)}$ = a past date, a researcher at the future date T_1 might use human biological material collected by another source between times T_0 and T_1. Assume that the researcher has no information about the methods of collection of such material. At T_1, then, should the researcher view the material as "existing" within the meaning of § (b)(4) and therefore excepted from the requirements of 45 C.F.R. Part 46?

It seems that the answer to this question should be "no." Human biological material collected after the date of effectiveness of governing regulations (T_0) should be collected in accordance with the regulations. Therefore, research at time T_1 on stored human biological material that was collected before the date of the regulations (between times $T_{(-1)}$ and T_0) might continue as a matter of policy, regardless of the available information on the collection of such material. Research on human biological material collected between times T_0 and T_1, however, should only be conducted if the researcher has information that indicates the material was

collected in accordance with the regulations. Otherwise, there would be no *ex ante* incentive for a researcher to collect human biological material in accordance with the regulations. If samples collected after the regulations are in effect are unusable if not identified as compliant, the collectors would have incentive to comply with regulations.

Finally, the § (b)(4) exception from the Common Rule applies only to research involving "existing" human biological materials; research involving the future collection and/or analysis of such material remains within the regulations' purview.

Another issue arises in interpreting the § (b)(4) exception for information that is "recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." A plain-language interpretation of this phrase would seem to yield the conclusion that all existing samples of human biological material that are not anonymously collected are identifiable, to a greater or lesser extent, and therefore are not excepted from regulation by § (b)(4). Again, however, definitional issues complicate interpretation of the regulations.

The term "identifiers" as used in § (b)(4) [exempting research involving 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"] is generally interpreted to include such items as one's name, social security number, mother's maiden name, etc. Questions arise when considering whether § (b)(4) could be interpreted to include, for example, encryption codes as a method of identifying the source(s) of human biological material. If not, an investigator's use of encryption codes only would qualify for the exception from regulation under § (b)(4).

If encryption codes were assigned to samples in the first of a two-step research process involving, perhaps, a person who collects and encrypts samples in step one and an investigator who conducts research using the samples in step two, the "information . . .recorded by the investigator" could be interpreted as consisting solely of the encryption codes. An information "wall" between collector (step one) and "investigator" (step two) could (if constructed properly) insulate the "investigator" from any and all information linking human biological material to research subject. The force of this argument would necessarily be contingent on the integrity of the "wall" (i.e. the ease or difficulty with which one could permeate the wall).

The argument can be made that federal regulations categorize human biological materials

based on their identifiability as used in research rather than the manner in which they are stored. Section (b)(4) suggests that, in determining the identifiability of material, one should look to the manner in which information is recorded by the investigator, indicating that the regulations could be consistent with a system of classification alternative to that used in the statements analyzed in this chapter.[18]

Definitional issues also arise in interpreting the regulations with respect to the meaning of "human subject" and "research". Section 46.102(f) defines "human subject" as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." Private information includes:

> information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. 45 C.F.R. § 46.102(f)(2).

In an encryption scenario, it is unclear whether the identity of the subject from whom a specimen originated "may readily be ascertained by the investigator or associated with the information." Could one accurately consider the information possessed by the investigator as "individually identifiable". Since private information must be individually identifiable in order for obtaining the information to constitute research involving human subjects, the encryption scenario might be viewed as not even involving human subjects, thereby exempting such research from the requirements of 45 C.F.R. Part 46 altogether.

In sum, the most straightforward read of the federal regulations seems to indicate that only anonymous existing (as of the date of effectiveness of the regulations) samples of human biological material are entirely exempted from the requirements of 45 C.F.R. Part 46. The requirements might apply to research on existing samples that are not anonymously stored, and to all research involving the future collection of such samples.

Finally, in regard to the informed consent requirements of the regulations, 45 C.F.R. §

46.116(d) provides that:

> An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
>
> (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 practicably be carried out without the waiver or alteration; and
>
> (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Research conducted so that individuals can readily be identified may be considered to involve greater than minimal risk to the subjects' confidentiality interests. Such research, therefore, might include informed consent requirements as a matter of course. Alternatively, research conducted so that individuals cannot readily be identified (e.g., research conducted with anonymous samples), might not require informed consent.

It is of note that there are other scenarios wherein the regulations' approach to informed consent might be interpreted to allow for its waiver. If a firewall is constructed between the collector of the samples and the investigator, where the investigator's only knowledge regarding the samples is encrypted, the research might be considered to involve no more than minimal risk to the subjects' confidentiality interests. In such a scenario, waiver of the informed consent requirement might be consonant with the regulations. However, in the current research environment, no uniform policy or practice for creating such a firewall exists.

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1. No statements provide explicit justification for this method of categorization.

2. These definitions are adapted from those discussed by the American Society of Human Genetics "Statement on Informed Consent for Genetic Research" (Am J Hum Genet 1996; 59:471-4) and Clayton, E.W. et al Informed Consent for Genetic Research on Stored Tissue Samples. *JAMA* Dec. 13, 1995:274(22); 1786-1792.

3. L.Andrews and D. Nelkin *Lancet* 1998; 351: 56

4. [Full ASHG cite to be added] (*Am. J. Hum. Genet.* 1996; 59:471)

5. [Full NIH/CDC cite to be added]

6. [Full PRIM&R/ARENA Tissue Banking Working Group cite to be added]

7. [Full ACMG cite to be added]

8. Clayton, E.W. et al Informed Consent for Genetic Research on Stored Tissue Samples. *JAMA* Dec. 13, 1995:274(22); 1791

9. [Full National Heart, Lung, and Blood Institute cite to be added]

10. NHLBI p. 15

11. [Full Pathologist Consensus Statement cite to be added]

12. NHLBI p. 17

13. *See en. # NHLBI...*

14. *See en. # Path...*

15. AAMC

16. AAMC Comments on The Recommendations of the Secretary of Health and Human Services on the "Confidentiality of Individually-Identifiable Health Information"

17. Pathologist Consensus Statement p. 4

18. Similarly, the Secretary, HHS, utilizes a test of reasonableness in formulating a "description of identifiability": "Information is identifiable if there is a reasonable basis to believe that the information can be used to identify an individual. . . . Reasonableness may depend on a judgment based on what other information is known to be available to a recipient, and the amount of effort and time that would be needed to achieve a positive identification."[cite to be added Secretary Recommendations p. 15]