February 22, 1999: This is a draft report of the National Bioethics Advisory Commission. It therefore does not reflect final conclusions or recommendations of the Commission and should not be cited or referenced as such.

Chapter 5
Conclusions and Recommendations

The appropriate protection of human subjects whose biological materials are used in research is as necessary as such materials are valuable in advancing our understanding of disease and developing new therapies. The research value of human biological materials is considerable. However, this value should not always override the rights of individuals to be protected from possible adverse consequences of the research use of such materials, such as invasion of privacy, inappropriate disclosure of confidential information, familial conflict or emotional harm, discrimination, or stigmatization. In order to balance these various interests, the federal government has put in place a set of regulations that govern research involving human subjects, which extend to include these materials.

NBAC concludes that these regulations, somewhat modified and interpreted as indicated below, can continue to protect the rights and interests of human subjects while at the same time permitting important and well-designed research using human biological materials to go forward. In addition, additional efforts are required by the National Institutes of Health, the Office for Protection from Research Risks, the scientific community, specimen repositories, and others to ensure that those individuals who permit their human biological materials to be used in research do so with the assurance that their interests are being adequately protected. Public confidence in a system where such protections are in place are likely to increase the probability that individuals will continue to make available their tissue, blood, or DNA for research. This confidence may also translate into continued support for research generally.

As one looks ahead, however, the structure of human subjects protections must take into account the evolving nature of biomedical science and the increasing need of researchers to have

access to a certain amount of ongoing clinical data (which might be collected over long periods of time) about the person from whom the specimen was obtained. That is, it will be important to ensure that the policies, guidelines and other rules that govern the involvement of human subjects in research make provision for, under certain appropriate circumstances, that the research sample being used retain sufficient identifying information to ensure that important clinical information can be provided to the investigator, and in some cases, back to the research subject. Where identifying information exists, however, there must be an unambiguous system of protections to ensure that risks are minimized and that the sample source's interests are protected.

Because the current system of protections for research subjects is based on a policy of self-referral—that is, investigators must make the initial effort to submit protocols for review by an Institutional Review Board (IRB)—it is especially important that the regulations describing which protocols are subject to review are clear; and where they are not, that efforts be made to either change the language or offer clear instructions as to the best interpretation of those regulations.

To determine whether the current system of protections provides adequate protection for individuals involved in research on human biological materials, and whether additional guidance or regulation is required, NBAC systematically reviewed the existing Federal Policy for the Protection of Human Subjects (45 CFR 46, or the "Common Rule").[1] In particular, NBAC tried to identify the precise meaning of relevant terms and concepts in the current regulations in the

1. The protections provided by federal regulations currently apply only to: 1) research conducted or funded by one of the 17 agencies that have agreed to be subject to the Common Rule or by any other federal agency that has promulgated its own set of human subjects research rules; 2) research on an investigational new drug, device, or biologic governed by FDA regulations; or 3) research conducted at an institution that has provided in its "assurance" with the federal government that all research with human subjects conducted at the institution will be governed by the federal regulations whether or not the research is federally sponsored or comes under the purview of the FDA.

context of research using human biological materials; how those concepts apply when determining whether protocol review can be expedited or consent requirements waived; and the nature of informed consent when research relies on already existing materials versus research that requires new collection efforts. To aid its analysis NBAC also reviewed proposals and guidance prepared and published by scientific, medical, and lay organizations and by other countries regarding the obligation of researchers to human subjects or sources of specimens to be used in their research protocols.

Two separate but related considerations factored into NBAC's analysis of the current federal protections. The first consideration was the adequacy of the current regulatory language in providing clear direction to researchers, IRBs, and others regarding the protections required in order to conduct research using human biological materials. The second consideration was the recognition that the extent to which the language of the Common Rule is adequate may turn on an evaluation of the decisions that currently must be made by the investigator, the IRB administrator or full IRB, and in some cases, the repository or person in possession of the human biological materials. These decisions include whether, under current regulations, a particular activity under consideration constitutes research, whether it involves human subjects, whether a protocol is eligible for expedited review, and whether consent of the research subject or source is required.

NBAC concluded that, in some cases, the regulatory language is adequate but only if given a specific interpretation; therefore, clarification of the current regulations is required. There are numerous ambiguities in the language of the Common Rule; for example, it refers to terms which are not self-defining, such as "existing samples," "publicly available," "minimal risk," and "private identifiable information." As a result, there is confusion about the intended meaning of these terms and this has stymied investigators and IRB members who testified before NBAC. In still other cases NBAC concluded that the regulations themselves are not adequate to ensure the ethical use of human biological materials in research, thereby requiring some modification of the

regulations.

In developing its recommendations, NBAC also considered the roles and responsibilities of the research community and federal agencies in ensuring that important research goes forward with the necessary protection of human subjects. In this final chapter, NBAC presents its interpretation of several important concepts in the federal regulations and recommends ways to strengthen, clarify, and make more consistent the implementation of protections for individuals who have contributed—or who may in the future contribute—biological materials to the biomedical research enterprise.

Activities that are the Subject of NBAC's Conclusions and Recommendations

In order to trigger the regulations, an activity must be considered "research," as opposed to a clinical therapy. The current regulations and NBAC's recommendations do not apply to purely clinical uses of such materials, or to other activities such as quality control procedures, or teaching. Rather, the regulations and NBAC's recommendations apply to *research* defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (45 CFR 46.102(d)). *If research on stored materials is done solely as part of a clinical intervention, as might be the case in a pathology laboratory where a biopsy is being assessed to confirm a diagnosis, then the federal regulations, and NBAC's recommendations, do not apply.*

Activities that have both a clinical *and* a research component are covered by the federal regulations and by NBAC's recommendations. If, therefore, the samples are obtained as part of a clinical intervention, but are then used for research purposes, in most cases the regulations and NBAC's recommendations apply. Any research conducted with samples left over from a clinical intervention, therefore, is subject to the federal regulations, if the investigator or the investigator's

institution is subject to those regulations (see footnote 1) or if the laboratory's institution has voluntarily agreed not to supply samples for research without invoking the federal regulations. This has implications, to be discussed later, for the consent procedures used by healthcare institutions that anticipate research involving stored human biological materials collected primarily for clinical purposes.

Adequacy and Interpretation of the Existing Federal Policy for the Protection of Human Subjects

Several terms in the regulations were found by NBAC to lack clarity, and thus do not adequately provide the needed guidance for investigators, IRBs, and others. These terms include: "existing and publicly available," identifiable," "minimal risk," "rights and welfare," and "practicable."

Existing and Publicly Available

There are two conditions under which research with human biological materials may be exempt from the Federal Policy for Protection of Human Subjects:

1) the samples are existing and publicly available; or
2) the samples are existing and information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects (45 CFR 46.101(b)(4)).

NBAC notes that there is an additional condition permitting exemption that pertains specifically to the research use of existing (stored) materials from individuals who are no longer living. Current federal regulations define a human subject as a "living individual" (45 CFR 46.102

(f)) and therefore do not extend protections to individuals who have provided biological materials and are no longer living.[2]

The meaning of some of the regulatory language pertaining to exemption is not clear when applying the criteria to the research use of human biological materials, particularly with regard to the first criterion, i.e., that the samples are existing and publicly available. *NBAC interprets the term "existing" to mean any materials that are already collected, that is, "on the shelf" at the time the research is proposed.*[3] According to OPRR this includes data or materials already collected in research and nonresearch activities. This contrasts with samples that are to be collected at a later date as a part of the research protocol.

It is, however, the second condition of the first criterion for exemption—the reference to "publicly available"samples—that NBAC found to be more problematic. In response to an NBAC request for clarification OPRR defined "publicly available" to mean that "unrestricted access on demand (i.e., unrestricted availability subject only to limited quantities and/or related costs) may be considered a reasonable basis for claiming 'publicly available'."[4] In NBAC's view, however, this interpretation provides minimal guidance as it remains unclear which "public" is the subject (e.g., the general public, the scientific community) and whether "available" is the same as "accessible."

To illustrate, NBAC's examination of repository policies regarding access to collections revealed that the larger repositories, often cited in discussion as examples of "public collections," have in place "strict policies to ensure that cultures are distributed only to qualified organizations

2. If the source of the sample is deceased, then according to the regulations, there is no human subject and the regulations do not apply. As discussed later, NBAC believes that there might be circumstances in which research on samples of deceased individuals has implications for living relatives, and that human subjects might, in fact, be involved, triggering some level of regulatory oversight.

3. This interpretation is consistent with that of OPRR. See, for example, IRB Guidebook, pp. xxx

4. Personal communication from OPRR Director, Dr. Gary Ellis, August 25, 1998.

and researchers with legitimate and justifiable scientific uses for these materials."[5] Thus, the biological materials are available not to *anyone,* but are, in general, restricted to those who have a legitimate research interest in their use and presumably possess the capabilities to perform sophisticated scientific techniques that can reveal biological information about that sample or even clinical information about the person from whom it came. Moreover, some newer DNA databases, for example, those associated with the federally funded Human Genome Project, are constructed based on the assumption that such information *should be* available to any scientist wanting to investigate the basic structure or function of DNA. For example, the National Human Genome Research Institute implements a policy on the release of human genomic sequence data that requires that primary genomic sequence data should be rapidly released, within 24 hours of generation. Thus, although collections might be widely available to the research community, and appropriately so, it appears that they are infrequently available to any member of the public. *NBAC supports the view that the interests of those that supply these specimens are best protected by restricting access to these materials to researchers who are fully qualified to add to our biomedical and clinical knowledge base.*

In NBAC's view, while access to specimens is an important consideration in assessing appropriate levels of protection, a somewhat more important set of considerations relate to: 1) whether the specimens are stored with codes, links, or identifiers; 2) whether identifiable samples (coded or identified) are delivered to investigators seeking access; and 3) whether the repositories or retainers of the specimens require any assurance that the research will be conducted in a manner that will protect the rights and interests of the sources. [6]

NBAC spent considerable time discerning the appropriate interpretation of the second

5. American Type Culture Collection (ATCC), http://www.atcc.org/

6. In its review of policies and procedures of several repositories, NBAC found that, in fact, some repositories require from investigators a statement of research intent and an assurance of compliance with the regulations for the protection of human subjects (45CFR46), but it is not clear that this practice is widespread, especially among

criterion for exemption, "the samples are existing and information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects (45 CFR 46.101(b)(4))." What constitutes identifiability, and to whom, is a central consideration for minimizing risks to subjects and is therefore an important issue in the interpretation of the regulations.

Identifiability of Samples and Applicability of Federal Regulations

A key consideration in deciding whether the regulations apply is determining whether a *human subject* is involved. This determination may be conditioned by whether the identity of the sample source can be determined, either directly or through identifiers linked to the subject, from the investigator's records. Specifically, the regulations define a human subject 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" (45 CFR 46.102(f)(1)&(2)). Section 46.102(f)(2) defines "identifiable" to mean "the identity of the subject is or may readily be ascertained by the investigator or….associated with the information." OPRR interprets "identifiable" to include specimens with codes that, with the cooperation of others, could be broken in order to reveal the name of the tissue source.[7]

In the published academic and professional literature on the research use of human biological materials, the language used to describe the identifiability of research samples varies. Previous guidelines and reports have categorized specimens by the conditions under which they are stored (with or without identifiers), although current federal regulations permit investigators to access stored specimens, make them anonymous by removing identifiers, and then use them in research without seeking consent of the donor.

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smaller, more informal collections.
7. IRB Guidebook, pp.2-9.

Part of the confusion about the interpretation of the term "identifiable" arises from the fact that people sometimes refer to the state of the information attached to the biological material in the repository (i.e., the **specimen**) and sometimes refer to the material (i.e., the **sample**) and the accompanying information that is provided to the researcher. For example, the specimen might be identified in the repository but no identifying information is forwarded with the research sample sent to the researcher. This distinction is of considerable importance because the potential for both benefit and harm is greater when the sample is directly or easily linked to the person who provided the specimen, placing the burden of protection in different places, depending on who has access to the information (e.g., the researcher or the pathologist, or both). If samples are identifiable the potential exists for the investigator or a third party (e.g., insurer, employer) to contact the subject or act in some way that might affect the subject. For example, an investigator might want to contact an individual to gather more medical information, obtain consent for additional or different uses of the sample, inform them about the results of the study, or communicate findings that might be of clinical significance to that individual.

NBAC adopted the following definitions regarding the diverse status of human biological materials, depending on whether they are sitting in storage in a repository, or whether some of the material from a repository has been selected for research purposes.

Repository collections of human biological materials (i.e., specimens) are one of two types:

1. **Unidentified specimens** are those for which identifiable personal information was not collected or, if once collected, is not maintained and cannot be retrieved by the repository.

2. **Identified specimens** are those linked to personal information, such that the person from whom the material was obtained could be identified by name, patient numbers, or

clear pedigree location (i.e., their relationship to a family member, whose identity is known).

NBAC believes that a distinction should be made between the ability of the repository to link a specimen with individuals and the ability of the investigator to link samples with individuals.

Research samples are the collections of human biological materials provided to investigators by repositories. Such materials are of at least four types, which are differentiated by the amount of information that is conveyed to the investigator about the person from whom the sample comes. NBAC defines the different types as follows:

1. **Unidentified samples**—sometimes termed "anonymous"—are those supplied by repositories from an unidentified collection of human biological specimens.

2. **Unlinked samples**—sometimes termed "anonymized"—are those supplied by repositories from identified human biological specimens without identifiers or codes such that the ability to identify particular individuals via clinical or demographic information supplied with the sample, or biological information derived from the research that would be extremely difficult for the investigator, the repository, or a third party.

3. **Coded samples**—sometimes termed "linked" or "identifiable"—are those supplied by repositories from identified specimens with a code rather than a name or any other personal identifier such as a patient number, where the repository (or its agent) retains information linking the code to particular human specimens or where the extent of the clinical or demographic information provided with the sample is sufficient that the

investigator, the repository, or a third party could link the biological information derived from the research with material from a particular person or a very small group of identifiable persons.

4. **Identified samples** are those supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) sufficient to allow the biological information derived from the research to be linked directly, by the researcher, with the particular person from whom the material was obtained.

For the purposes of interpreting and applying the regulations, NBAC aggregates these four groups into two categories: 1) *unidentifiable samples*, which are either unidentified or unlinked (categories 1 and 2 above); and 2) *identifiable samples*, either coded or identified (categories 3 and 4 above). The recommended protections required within each category are the same.

Unidentifiable Samples. As mentioned above, within the "unidentifiable" category are two subcategories: 1) unidentified samples; and 2) unlinked samples. Unidentified samples have no data (even as specimens in the repository) linking them to an individual and, therefore, no one has the ability to determine the identity of the source of the specimen. Such samples are completely anonymous. In other cases, the samples may be "unlinked" or "anonymized," that is, the specimens from which the samples are derived retain identifiers but the samples are forwarded to a researcher without any identifiers or codes. NBAC considers these samples to be unidentifiable for the purposes of the regulations because neither the investigator nor anyone else can ascertain the identity of the person from whom the sample originated.

Several repositories keep a record of the persons from whom the samples came so that the repository can track that a sample was sent to a clinician or researcher. Such samples may be

numbered in such a way so that even the repository cannot link the sample to its source. Or, samples might be numbered in such a way that the repository can track that a sample was sent forward but if the investigator were to come back to the repository and ask for additional material or clinical information specific to that source the repository could not match the request with a specific specimen. At best, the repository could send the investigator a duplicate set of the initial "batch" of samples, but again with no linking data. There might be some rare cases in which the sample size is so small and the findings so unique that it would be relatively easy to identify individuals even if their samples were unlinked. Investigators and repositories should give these situations careful scrutiny to reduce the chance that persons could be identified. In such instances, it may be more appropriate to use only unidentified (not merely "unlinked") samples, increase the sample size, or even consider the samples to be identifiable rather than unidentifiable.

When researchers use unidentified and unlinked samples, contact of the source by the researcher is extremely difficult. According to the federal regulations, research using existing samples of this type is exempt from IRB review. The justification for this regulation appears to be that since it is not possible to contact the sources to ask their permission for any specific uses or to gain consent, and because the potential for harm effectively disappears due to lack of identifiability, no special restrictions of the use of such unidentifiable samples should apply.

Although this seems quite reasonable at first blush, some controversy remains in the case of samples that have been rendered unidentifiable before being sent on to the investigator. Some might consider it ethically problematic that by having identifiers stripped, the investigator loses the opportunity to obtain consent, since further recontact would be prevented. In addition, it is incorrect to assume that because the sources cannot be identified they cannot be harmed or wronged. There are some interests of the sample sources that may be harmed even if the sources are not completely identifiable, and there may be some interests of others at risk as well. For example, there might be group or family interests that could be revealed or placed at risk because

of research done on a class of similar, albeit individually unidentifiable, samples. Individuals have an interest in avoiding uses of their tissue that they regard as impermissible or objectionable on moral grounds. Thus, were their samples to be used in research that they would find objectionable then it is possible that some individuals could be wronged, if not harmed. NBAC recognizes these concerns as valid but not sufficiently substantial to restrict further use of such samples.

Because the samples are not linkable to individuals, some of the most important interests that weigh in favor of restricted access do not apply. If the individual cannot be identified, then there is little or no risk of insurance or employment discrimination, stigma, adverse psychological reactions, or familial conflict. So to that extent, the case for not allowing use of unidentifiable stored samples is significantly weakened. The possibility remains that research findings might still result in potential harms to groups or classes of individuals (e.g., loss of health insurance coverage for individuals found to share a particular trait or characteristic). Although the current regulations do not require investigators to consider such risks to groups, good practice might, in some cases, warrant an effort to minimize risks to others through consultation with relevant groups, alterations in research design, or greater care in the manner in which research results are reported.

Given the importance of society's interest in treating disease and developing new therapies, a policy that severely restricted research access to these unidentifiable samples would severely hamper research and could waste a valuable research resource.

Identifiable Samples. Within the "identifiable" category are two subcategories: 1) coded samples; and 2) identified samples (i.e., where the sample source is expressly identified to the investigator). Within the first category there may be a distinction between the information provided to the investigator and that held by the repository. For example, the samples might be encoded in such a way that the investigator cannot identify the sample source but the entity storing the sample, such as a pathologist or DNA bank, can link the sample source to the

specimen sent to the investigator. Thus, the code could be broken if desired. Although identifying the source may be more difficult in this latter scenario, NBAC considers these samples to be identifiable, because the possibility of linkage remains, elevating the potential for harm. The ease of identifying the source is part of the calculus in determining the overall level of risk posed by the research. This matter is discussed later.

Previous guidelines and reports (see Chapter 4) have categorized samples by the conditions under which they are stored (with or without identifiers). Current federal regulations permit researchers to take existing samples, render them anonymous by removing identifiers, and then use them in research without seeking consent. It is apparent to NBAC that some investigators incorrectly interpret the regulations to mean that as long as **they** do not know the identity of the sample source, even if the sample is coded (linked), the research is exempt from IRB review. The issue of identifiability is further confounded by the researcher's growing ability to identify the source (even when unidentified) because of the possibility that DNA analysis will permit matching of samples with individuals. *NBAC concluded that the policy would better protect human subjects, while still preserving the scientific value of the samples, if someone independent of the investigator coded the samples or rendered them unidentifiable, for example the repository, an encryption service, or someone at the research institution who is not directly involved in the conduct of the research in question.* NBAC recognizes that there may be costs associated with this requirement. Thus, any costs incurred by the investigator to satisfy this requirement should be considered by the funding agency a valid and reimbursable expense.

NBAC does not believe that these interpretations of the criteria for exemption and review will impede research. In fact, some repositories already have in place these protections and many investigators voluntarily elect to have repositories strip identifiers before samples are sent forward to their laboratories. These interpretations will ensure that research conducted on identifiable samples, even if widely or publicly available, will be subject to the federal policy of protections.

Criteria for Waiver of Consent

The adequacy of the requirement of informed consent to provide appropriate protections should be evaluated in terms of whether or not it achieves its intended goal. The purpose of informed consent in research is to provide potential subjects with materially relevant information about the purpose and nature of a proposed study, and appropriate information about risks and benefits to enable persons to make a voluntary decision regarding participation. In considering the conditions for which informed consent should be required for the research use of human biological materials, NBAC recognized that informed consent, *by itself*, cannot provide protection for all the legitimate interests at stake in the practice of gathering and using biological samples. Instead, informed consent plays an important but not exclusive role in safeguarding both human subjects and research interests. Of course, consent can never by itself protect someone from harm: it can only provide individuals with available information about the probability and magnitude of harm. Overly elaborate consent requirements cannot guard against all harms to subjects, would be extremely costly, and could constrain socially valuable scientific research.

As stated in the current federal regulations, human subjects research is presumed to require consent, but this requirement can be altered or waived if all four criteria, set forth at 45 CFR 46.116(d), are met.

1) the research involves no more than minimal risk to the subjects;
2) the waiver or alteration of consent 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.

Determining the risks of research and the effects that waived consent might have on the rights and welfare of the subject are bedrock considerations in deciding the level of protection required for human subjects in research. Determining the level of risk to the subject is a key criterion in deciding eligibility for expedited IRB review and in assessing the need to obtain informed consent from the subject. Four key terms are central to this determination: "minimal risk," "rights and welfare," "practicability," and "after participation."

Minimal Risk. The regulations state that "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests" (45 CFR 46.102(i)). Determining whether research risks are minimal thus depends upon a comparison of research risks with risks which persons "ordinarily" face outside of the research context.

However, when considering the risks of research conducted on human biological materials, one can question the applicability of the threshold that the regulations establish for assessing minimal risk. The risks encountered "during the performance of routine physical or psychological exams or tests" have limited utility as a baseline. While these risks can be compared to the physical risks faced in the collection of new samples, they are not really comparable with the risks of social and psychological harm relevant to research on biological samples. The risks encountered *"during the performance"* of a medical exam evidently relate to harms which the intervention itself may produce. The risks of psychosocial harm associated with research on biological samples, on the other hand, relate to future uses of information derived from samples.

The risks of "daily life" seem a more promising threshold for assessing the risks of research on biological materials. In research on biological samples, the potential harms of central

concern (e.g., stigmatization, insurance and employment discrimination, familial conflict, anxiety, violations of privacy) are those which can result if certain information from biological samples (e.g., the subject's susceptibility to disease) is disclosed to non-investigators. But such information is also commonly contained in medical records. Persons (research subjects and non-research subjects alike) generally face the risk that diagnostic, predictive, and other forms of information about them contained in their medical records will be obtained and used in a harmful manner. Although there are insufficient data to make a decisive statement about the relative probabilities of harm resulting from uses of biological samples vis-a-vis access to medical records, one might hold that the level of risk is similar in both cases. Indeed, research on biological samples arguably poses lesser risks, since the sources of even "identifiable" samples may be more difficult to trace than the subjects of explicitly labeled medical records. Thus, one might conclude that most research on biological samples is "minimal risk."

NBAC does not find this analysis of "minimal risk" to be compelling. On this reading of the regulations, the issue is not fundamentally whether the risk of harm which research poses to subjects is in itself minor or substantial; rather, the issue is whether the risks the research presents are more severe than risks which persons ordinarily confront outside of research. On this interpretation, research risks could be substantial but nevertheless count as "minimal." The problem is that the purpose of assessing whether risk is "minimal" is to help IRBs determine what types of protections should be required. While a strict reading of the regulations may permit an interpretation which permits one to deem great risks of harm to subjects "minimal," such an interpretation certainly violates the spirit of the regulations.

An alternative interpretation of the regulations avoids this result. On this interpretation, "'risks of everyday life,' has normative as well as descriptive force, reflecting a level of risk that is

not simply accepted but is deemed socially acceptable."[8] According to this account any risk that is not socially acceptable cannot properly be characterized as a risk of "daily life." There is a widespread view that the present risks of harm from uses of sensitive medical information about individuals are not acceptable, and that we need stronger privacy laws to remedy this situation. Thus, the risks of harm resulting from the improper use of medical records are not, on this interpretation, risks of "daily life." It follows that one cannot employ the risks of harmful uses of medical records as a baseline for determining whether research on biological samples is minimal risk. This, in turn, makes it difficult to perform a minimal risk analysis for research on biological samples, as there are no apparent alternative candidates that can plausibly serve as a baseline.

While the regulatory definition of "minimal risk" thus appears inadequate for research on human biological materials, the additional requirement that the waiver of consent must "not adversely affect the rights and welfare of the subjects" (45 CFR 46.116 (2)(d)(2)) is sufficient to protect the same interests. As discussed below, the rights and welfare condition for waiver or alteration of consent requires an assessment of the risks of psychosocial harms and protects subjects from any substantial risks.

Rights and Welfare. Failing to obtain consent may adversely affects the rights and welfare of subjects in two basic ways: (1) The subject may be improperly denied the opportunity to choose whether to assume the risks that the research presents; (2) The subject may be harmed or wronged as a result of their involvement in research to which he or she has not consented.

A waiver of consent in the collection of *new* biological samples violates subjects' rights because it would expose them to unwanted bodily invasions. The interest in being free from unwanted bodily invasions is the primary interest the requirement of informed consent was

8. Benjamin Freedman, Abraham Fuks, Charles Weijer, "In loco parentis: Minimal Risk as an Ethical Threshold for Research Upon Children," *The Hastings Center Report*, Vol. 23, No. 2, p.x, March, 1993.

instituted to protect. In the case of consent for the use of *existing* samples, the interests at stake are different. In this context, it is principally the social and psychological harms delineated in Chapter 3 that are at issue. Subjects' interest in controlling information about them is tied to their interest in, for example, not being stigmatized or not being discriminated against in employment and insurance. The degree to which the assertion of these interests is compelling is a function of the probability of harm occurring. Important considerations that figure into the probability of harm occurring, include:

(1) How easily is the sample source identifiable?
(2) What is the likelihood that the sample source will be traced?
(3) If the source is traced, what is the likelihood that persons other than the investigators will obtain information about the source? (Privacy/confidentiality laws may be relevant here, as is the integrity of investigators and their institutional confidentiality protections.)
(4) If non-investigators obtain the information about the source, what is the likelihood that harms will result, including adverse consequences arising from the reporting of uncertain or ambiguous clinical results? (State and federal discrimination laws may be relevant with respect to uses of information by third parties).

As noted in Chapter 3, the probability of psychosocial harms resulting from research on biological samples is somewhat speculative at present. There are, however, good reasons to think that the risks of harm are generally minimal, or at least can easily be rendered minimal. Given current scientific practices, there are few studies where it is necessary that investigators know the identity of sample sources. Thus, investigators will not usually have a need to trace sample sources although they might require additional clinical information without identifying the source. Even where investigators do trace a source, it is not necessary to reveal information about sources to third parties. While it is nonetheless possible that non-investigators will access information about a source, investigators can minimize this risk through appropriate confidentiality

mechanisms. For example, protocols that include provision for a way to isolate the results of genetic or other research results completely from the subject's medical record, and that incorporate a prohibition on returning uncertain or ambiguous information to subjects (which would forestall the communication of premature and potentially upsetting information) should in most cases ensure that risks will be minimal.

Although the risks of psychosocial harms may generally be minor in research on human biological materials, there are some important exceptional cases. For example, controversial studies such as those which involve behavioral genetics or which make explicit comparisons between ethnic or racial groups, are likely to offend some research subjects and threaten their ascriptive identity. Moreover, there remains the likelihood that the results of such studies will be used to stigmatize and discriminate against group members (research subjects and non-research subjects alike).

Practicability. An investigator who requests a waiver of the informed consent requirement for research use of human biological materials under the current federal regulations must provide to the IRB evidence that it is not practicable to obtain consent. Neither the regulations nor OPRR offer any guidance on what defines practicability.[9]

Practicable is defined in the ordinary sense as that which "can be done or used," or is "possible in practice" (*Oxford English Reference Dictionary*). This could suggest that obtaining consent is always practicable, so long as there are the means and skills to carry this out, but that it can never be an absolute requirement. The issue for regulatory purposes, and, NBAC would suggest, for the purpose of assessing the ethical acceptability of this provision, is whether the practicability requirement—alone or in combination with other criteria for obtaining a waiver—adds guidance to the investigators and IRBs who will make these decisions. Informed consent

9. Personal Communication, Dr. Gary Ellis, Director, OPRR, August 25, 1998.

may not be "possible in practice" when there are many more subjects than there are individuals to seek their consent, or when the amount of time it would take to recontact would be longer than the period of time the study was to take place. Similarly, obtaining consent might be thought of as impracticable if the financial costs either of a direct recontact effort, or even indirect efforts (such as mailing consent forms and information) far exceeded the researcher's budget. One might even suggest that in research that is designed to hold out the prospect of direct benefit to some of the subjects, it would be impracticable to take the time to recontact potential subjects because the delay in completing the study could be thought of as a more serious harm than the failure to obtain express consent. While these are reasonable examples of impracticability, and, NBAC would suspect, might be regarded by some as good reasons for granting a waiver, the trouble with the practicability requirement is that it forces a comparison between otherwise incommensurable harms: the wrong that could be committed by not obtaining informed consent, and the prohibitively costly, perhaps difficult, and even needlessly intrusive harm of attempting recontact. As with many types of incommensurability in IRB review the customary task of assessing risk and benefit becomes far more problematic.

Even where it might be deemed practicable to obtain consent for research use of stored human biological materials, it may be unnecessarily burdensome for investigators. *NBAC believes that in assessing the appropriateness of waiving consent, consideration should be given principally to the criteria of minimal risks and rights and welfare. Practicability should not be a compelling consideration.*

Providing Additional Information as Required at 45 CFR 46.116(d)(4) In the current regulations, the third condition for the waiver of consent stipulates that, "whenever appropriate, the subjects will be provided with additional pertinent information after participation." The historical context for this condition are "deception" studies (e.g., the behavioral sciences) in which it is deemed crucial to study design that the individual not know of

their status as a research subject. Thus, according to the regulations, the IRB, while waiving consent (by finding and documenting the first three required conditions), could require that subjects be informed that they were subjects of research, a so-called "debriefing" requirement.

The applicability of this condition in the context of stored samples could be interpreted in a variety of ways. If the first three conditions of waiver of consent are met, the IRB might require, as an additional measure of protection, that the investigator provide further information to the subjects. Such a communication would describe the status of the research project and inform them that their samples will be used or were used in the research. Such a requirement might only be appropriate if consent had already been obtained and the IRB determines that re-consent is not required for a specific or new protocol. The IRB might well recognize that only those subjects who could be found would be so informed. *NBAC interprets that "after participation," a term originally intended to apply to deception studies, could refer to after the sample is obtained, rather than exclusively to the period after the research is conducted. In general, however, NBAC concludes that this fourth criterion for waiver on consent is not relevant to research using human biological materials, and, in fact, might be harmful if it forced investigators to recontact individuals who might not have been aware that their materials were being used in research.*

"Opt Out" as an Additional Measure of Protection when the Consent Requirement Has Been Waived

"Opt out" refers to the choice given to a subject to exclude themselves from a study. Unless someone has "opted out," they are assumed to be enrolled. If, after a waiver of the consent requirement is granted, an investigator or IRB has residual concerns about the nature of the research or the possibility that some individuals might find the research objectionable, then an additional measure can be taken to allow subjects to opt out of the research. In this scenario,

subjects would, if possible, be contacted and given the choice of opting out; if they did not respond or could not be found, the sample could still be used because the consent requirement had already been waived. This differs significantly from a scenario in which the consent requirement has not been waived. In that scenario, if a person did not respond with explicit consent or could not be found, their sample could not be used in the research protocol.

Obtaining Informed Consent

Specimens that already exist in storage at the time the research is proposed may have been collected under a variety of conditions (e.g., in a clinical setting or as part of an experimental protocol). In some instances, individuals make informed choices about how their sample should be used subsequent to its original research or clinical use. In other cases, for a variety of reasons, individuals may not fully understand or have not been given the opportunity to carefully consider and decide how their sample may be used in the future. When research is contemplated using existing samples, the expressed wishes of the individuals who provided the material must be respected. Where consent documents exist, they may indicate whether individuals wanted their sample to be used in future research, and in some instances the specific type of research.

IRBs should use the following criteria to evaluate the applicability of such documents to the proposed research:

- Does the language or context of the consent form indicate that the source was interested in aiding the type of research being proposed?

- If the person consented to the sample being used in unspecified future studies, is that consent adequate for the type of research being planned, given the circumstances under which the sample was collected (e.g., whether the sample was requested by a treating physician, whether

the consent form offered alternatives to allowing the sample to be used in future studies)?

In some cases an IRB may determine that an existing consent form permitting unspecified future uses to be sufficient. For example, Clayton and colleagues argue that, "[e]ven in the absence of specific language about DNA testing, it may be appropriate to infer consent if the source wished for the sample to be used to determine why his or her family had a particular inherited disorder (1995)." In such cases, investigators should consider informing subjects that research is occurring and in certain cases also give them the opportunity to "opt out." Rarely, however, does the language in typical operative and hospital admission consent forms provide an adequate basis for inferring consent to future research.

A policy that provides significant protection for sources and recognizes that their samples may have been collected without adequate disclosure, yet which does so without depriving them—without their consent—of possible life-saving benefits of future research would be as follows. Where an existing sample is identifiable, and the IRB determines existing consent documents to be inadequate, the individual can be offered the option of consenting to the specific proposed protocol, and further offered the option of deciding how the sample may be used in the future.

As in the case with research in which new samples are obtained, individuals should be provided with relevant information to assist them in making a decision about participation in research. Federal human subjects regulations list the basic elements of informed consent which, of course, apply also when consent is requested for the use of existing samples (45 CFR 46.116[a]). The following points are especially relevant here:

a) The risks and benefits of participation in the proposed study along with a discussion of the possible consequences of consenting to future identifiable uses of their sample.

b) The extent, if any, to which confidentiality will be maintained. (Investigators are encouraged to seek certificates of confidentiality, when appropriate.)
c) Under what circumstances, if any, subjects will be re-contacted.
d) An indication that if subjects choose to have their sample rendered unidentifiable they cannot be given specific information about findings related to their samples.

The rationale for including the option of authorization for future research use of existing samples rather than mere disclosure that the sample may be used for a wide range of purposes is that in most cases existing samples will have been collected without disclosure. Allowing persons (whose previously collected samples are identifiable) to choose either to authorize future research use or to have their samples rendered unidentifiable for future uses can be viewed as an effort to repair this deficiency. Even if such authorization bears only a remote resemblance to genuine informed consent, it can serve as an expression of respect for persons in the context of proposed uses for existing samples. Simply to disclose to persons now that the sample already taken from them may be used for purposes of which they had no idea at the time of collection is not adequate.[10]

This policy for existing samples should be supplemented with special attention to areas of research considered sensitive or potentially objectionable to some. In other words, if the source of an identifiable existing sample chose the option of not rendering the sample unidentifiable and authorized future identifiable research uses, he or she would enjoy the additional protection afforded by the requirement of specific consent for uses of the sample that might be considered sensitive or objectionable. Such a category might include, for example, certain behavioral genetics protocols, studies differentiating traits among ethnic or racial groups, or research on stigmatizing characteristics such as addictive behavior.

10. Elsewhere, NBAC has discussed the issue of prospective authorization and found that under some circumstances it is an important method of respecting individual choices (see "Capacity," p.61). NBAC does not

Appropriate criteria should be used to determine whether re-contacting the individual is the appropriate course of action. Additional concerns should be addressed when developing a plan to recontact any individuals. For example, if explicit consent was never obtained for use of a sample (because it met the requirements for waiver), IRBs should consider potential harms that might arise should a subject learn, after the fact, that his or her material had been used in an experiment, unbeknownst to the them.

Obtaining Consent in the Clinical Setting

When samples are collected, whether in a research or clinical setting, it is appropriate to ask subjects for their consent to future use of their sample, even in the case where such uses are at the time unknown. The elements of the consent process for new samples should be the same as those discussed previously for the use of existing identifiable samples.

There has been discussion in the literature and in testimony given before NBAC of the concerns that arise when administering a consent process in a clinical setting (Transcripts Dec 9, 1997). These concerns often note that the clinical setting, where stress may be high, may not be conducive to a consent process that involves complex choices about issues not directly related to clinical care, and which involve thinking about the distant future. In this setting individuals may be anxious about the clinical procedure and may not be prepared to consider carefully the factors that go into making informed decisions about hypothetical research use of their tissue. The fact that individuals will also be faced with other decisions and paperwork related to the clinical procedure compounds the problem of administering an informed consent process in this setting.

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regard prospective authorization as valid for enrollment in research, but recognizes its moral value.

Another way of improving the consent process may be to inform individuals about, and ask for their consent to, future research use of their sample at some point before or after consent is obtained for the clinical procedure. More studies should be done on the issue of the best time to administer this consent in the clinical setting. NBAC acknowledges the important contribution to this discussion of groups such as the National Action Plan for Breast Cancer, which has done thoughtful work on ways to improve the overall consent process, including the timing of obtaining consent. As investigators and IRBs consider this issue, it may be useful to consult the work of groups who have made helpful suggestions regarding the design and timing of the consent process. Using such guidance and their collective experience, the scientific community should develop a consensus around a standard method for human biological material collection in both therapeutic and research contexts that would minimize the need for complex recontact efforts.

Rendering Existing Identifiable Samples Unidentifiable to Avoid the Need for Consent

A more practical solution to using existing samples for which it is impracticable or problematic to gain express informed consent for a specific use of the sample is to render the samples unidentifiable. The rationale for this apparently simple proposal is that in many cases existing samples were collected without anything resembling adequate disclosure that they would be used for a range of purposes unrelated to the context in which they were collected.

There are several drawbacks to rendering existing samples unidentifiable for every use that is not specifically consented to by the source. First, there is the administrative cost of rendering such samples completely unidentifiable. Second, if a sample is not identifiable, opportunities may be lost to protect the well being of the source or his or her relatives (e.g., in the case of genetic conditions) when later research discovers therapeutically significant links between various diseases or between diseases and genotypes. Third, rendering a sample unidentifiable restricts the

usefulness of that sample to investigators, who might wish to obtain additional samples, or who might wish to gather additional medical information from the patient or the medical record. Thus, there could be a scientific or medical price to pay for this action. Fourth, some investigators may choose to render identifiable samples unidentifiable so as to avoid the time and cost of IRB review and the possibility that the IRB may require obtaining informed consent.

Another possible ethical objection to this practice is based on the belief that rendering existing samples unidentifiable without consent is problematic because researchers once had the opportunity to seek consent but did not exercise it.

NBAC believes that rendering existing samples unidentifiable in order to expedite research protocols can be avoided in many situations by designing the research in such a way as to minimize risks to the subjects. If risks are minimal, then it is possible that the requirement for informed consent might be waived or altered according to the regulations, 45 CFR 46.116(d). If the nature of the research changes in the future, so that an investigator now selects specific samples for additional studies that might increase risks beyond the minimal level, further IRB review would be required.

Moreover, for future sample collection, a consent process that is explicit about the identifiability/unidentifiability of the sample source (see discussion below) will help to alleviate the need for the investigator to use unidentifiable samples.

Nevertheless, the NBAC recognizes that there will be some situations in which it is scientifically sound or desirable to render samples unidentifiable, and there is no scientific or medical cost to doing so. In addition, NBAC recognizes that going back to seek consent could be costly and time consuming in situations where there is a small possibility for stigmatization or harm once the identifiers are removed. Furthermore, contacting individuals might be disruptive

and even unwanted by the sample source. *With these considerations in mind, NBAC concludes that, in those circumstances where valuable samples could not otherwise be used, where consent would be difficult to obtain, and where there is no scientific cost to losing the link, it is ethically acceptable to render samples unidentifiable without the source's consent.* In arriving at this conclusion, NBAC also considered public input it received during deliberations, in which most people emphasized that they did not view their donated biological material as something that belonged to them, but rather as a gift to be used by the scientific community subject to the review for quality and ethical acceptability, and if they could be assured that the information obtained would not be used to discriminate against them.

Reporting Research Results to Subjects

Experts disagree about whether interim or clinically inconclusive findings from research should be communicated to subjects, although most agree that such findings should not be conveyed because only confirmed, reliable findings constitute clinically significant or scientifically relevant information. Persons who oppose revealing interim findings argue that the harms that could result from revealing preliminary data are serious, including anxiety or unnecessary (and possibly harmful) medical interventions. They prefer to avoid such harms 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 unforeseen limitations" [p. 3]. 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 the principle of

autonomy dictates that subjects have a right to know what has been learned about them, and therefore, that interim results should be shared with subjects (Veatch).

Reilly (1980) suggests that IRBs develop general policies governing the disclosure of information to subjects to help make these determinations. At least the following three factors should 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 findings: 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].

Considerations of Potential Harms to Others

The federal regulations governing the protection of research subjects extend only to individuals who can be identified as the source of the biological samples. The exclusive focus of the regulations on the individual research subject is arbitrary from an ethical standpoint, since persons other than the subject can both benefit and be harmed as a consequence of the research.

Risks to Groups

Research on samples that implicate groups may place group members at risk of harm. For example, research revealing that a racial or ethnic group is unusually prone to disease could be used to stigmatize and discriminate against group members.

OPRR guidance to IRBs and investigators on how best to identify and minimize risks to groups is required. Consultation with group members prior to designing and implementing research on groups, for example, may often be an effective way to understand and reduce risks to groups. However, work needs to be done to identify appropriate mechanisms for group consultation.

It also seems appropriate to highlight how some of these issues ought to be discussed among researchers and their professional organizations. For example, what is the appropriate role of public health policy in developing new knowledge from genetic epidemiology? Will additional ethical considerations be adjusted to ensure that the benefits of public health objectives do not come at the cost of individual concerns? For many studies, the answer may be yes: the net gain to a particular "population" from knowing about its increased risk (especially when something can be done at an individual level with this knowledge) will often outweigh the harms that come from labeling a group as "high risk."

Risks and Potential Benefits to Relatives of the Sample Source

Others who may be at some risk are first-degree relatives, or next-of- kin. The need to consider these people "at risk" is particularly evident when the disease or condition being studied is genetic (and thus may be shared by family members) or diseases that involve infectious agents or toxic exposures. In these instances, investigators are likely to be fully aware that the research they are conducting on a sample might have implications for those closely related to the sample source, individuals who are readily identifiable.[11] NBAC does not assume that because there might be risks to relatives of the sample source, those risks warrant considering those individuals

11. This distinction is worth noting. In the case of membership in a group, persons might not be individually identifiable although identified as a member of that group. In the case of biological relatives, persons related to the

to be human subjects, deserving the protection of informed consent.[12] In fact, NBAC finds the possibility that a relative of the sample source could stop a research protocol on the basis of consent not only impractical, but also troublesome. If the sample source has consented to the research use of his or her sample, that consent alone is sufficient for the research to proceed. However, although the regulations do not require that the concerns of first-degree relatives to be considered, NBAC recognizes that there might be circumstances in which an investigator finds it useful, beneficial, appropriate, and feasible to consider potential harms and benefits with such individuals.

A different set of concerns arise when the source of the sample is deceased. Under the federal regulations, people are human subjects only while living. Research involving human biological materials from individuals who are deceased at the time of the research is not subject to the requirements of DHHS regulations, regardless of whether or not prior informed consent was obtained. In addition, the existing regulations do not make explicit the status of living relatives of deceased individuals whose stored samples are used in research.[13] However, it is possible that the living relatives of the deceased sample source might have an interest in the research, particularly if the investigation focused on hereditary traits.

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sample source are likely to be individually identifiable.

12. OPRR has indicated that the living relatives might in fact be considered human subjects by virtue of their genetic relationship to the sample source, but the regulations—specifically the *OPRR Institutional Review Guidebook* section on human genetic research (pp. 5-42 to 5-63)—do not clearly specify how this consideration is to be handled by IRBs.

13. Please note 45 CFR 46.102 "Definitions: (f) Human subject means 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 . . ." (OPRR Reports, Protection of Human Subjects, 1991).

15. This interpretation is consistent with the current OPRR interpretation of the federal regulations.

Public and Professional Education and Conduct

Public and professional education is an essential part of effective public policy on the use of human biological materials for research. By education, NBAC is referring not simply to the provision of information with the aim of adding to the net store of knowledge by any one person, or group; rather, education refers to the ongoing effort to inform, challenge, and engage. Education about ethical issues in research involving human biological materials means that a variety of individuals and groups would have new tools to assess these important issues. Therefore, opportunities for such education need to be directed to IRBs, researchers, other members of the research and academic community, political decision makers at the state and federal levels, interest groups, possible human subjects and the eventual consumers of research on human biological materials. There must be widespread and continuing deliberation and the provision of information and education to the public in the area of genetics, and on other developments in the biomedical sciences, especially where these affect important cultural practices, values, and beliefs.

These discussion should encompass the kinds of issues raised by storage and use of human biological materials and the implications of such research on important values. Moreover, as it is the research community that seeks access to these materials, for policy purposes a moral burden should fall on researchers to elicit from prospective contributors, both individual and communal, the values and meaning they attach to the requested samples.

Recommendations

The goals of these recommendations are to: (1) address perceived difficulties in the interpretation of federal regulations, and in the language of some professional organizations; 2)

ensure that research involving human biological materials will continue to benefit from appropriate oversight and IRB review, the additional burdens of which are kept to a minimum; 3) provide investigators and IRBs with clear guidance regarding the use of human biological materials in research, particularly with regard to informed consent; 4) provide a coherent public policy process framework for research in this area that will endure for many years and be responsive to new developments in science; and 5) provide the public (including potential research subjects) with increased confidence in the research activity. To accomplish these goals, NBAC makes 24 recommendations in the following areas:

- applicability of federal regulations
- waiver of consent
- use of stored samples
- research design
- informed consent
- publication and dissemination of study results
- education and research support
- federal and state legislation on medical record privacy

Recommendations Regarding Applicability of Existing Regulations

NBAC recommends that current federal regulations governing human subjects research be interpreted as follows:

1. **When federal regulations governing human subjects research (45 CFR 46) are determined to apply for research involving human biological materials, these regulations should be interpreted by the Office for Protection from Research Risks, other federal agencies who are signatories to the Common Rule, Institutional Review Boards, investigators, and others, in the following specific ways:**

a) Research conducted on *existing* human biological materials is exempt from regulatory oversight when the materials are either unidentified as stored specimens or rendered unidentifiable for research purposes by someone independent of the investigator. The Office for Protection from Research Risks should issue appropriate guidance for investigators and IRBs on this exemption or, if deemed necessary, modify the language of the regulations ("the Common Rule").

b) Research using *existing* human biological materials that are publicly available is exempt from IRB review, as per the regulation set out at 45CFR46.101(b)(4). NBAC recommends that the phrase "publicly available" be interpreted to mean .....[nb: the commission needs to fill this out]

c) Research conducted on *existing or future* collections of human biological materials that are linked, even through a code, to information that could identify the individuals from whom they were obtained is subject to the process of review and approval specified by the Common Rule (see 45CFR46.101(b)(4)).[14]

Recommendations Regarding Waiver of Consent

Investigators who are subject to IRB review and who seek a waiver of the requirement for human subject consent should be given the benefit of clear guidance concerning key criteria for such a waiver. A significant consideration is whether the research is minimal risk, a concept that is ill-defined by the existing guidelines in the context of research using human biological materials. Moreover, the meaning of "adverse affects on rights and welfare" is not well described in existing regulatory guidance. Finally, the third and fourth criteria for waiver of consent concerning practicability and need to debrief subjects should not apply to research using human biological materials.

2. The criteria for determining whether informed consent can be waived under 45 CFR 46 116(d) should be interpreted by Institutional Review Boards and investigators in the following ways:

a) IRBs should, in general, operate on the presumption that research on *existing* coded samples is of minimal risk to the human subjects if: 1) the study makes provision for maintaining the confidentiality of the research results; 2) the study design incorporates a plan for whether and how to reveal findings to the sources or their physicians; and 3) the study involves examination of traits that are not commonly of political, cultural, or economic significance to the community or the sample sources.

b) The term "adversely affects the rights and welfare" of human subjects should be interpreted to mean that the waiver of consent does not violate any state or federal statute regarding an entitlement to privacy or that it does not involve revelation of information to any third party with an interest in the employment or insurability of the human subject.

c) If research using *identifiable existing* human biological materials is determined to present minimal risk to subject's rights and welfare, the consent requirement may be waived without meeting the practicability requirement (45CFR46.116(d)(3)). This requires a change in the federal regulations for this category of research. In the interim period before such a regulatory change occurs, NBAC recommends that OPRR issue guidance to IRBs emphasizing the importance of according more weight to considerations of risk and rights and welfare and less to the ease of obtaining consent.

d) The Office for Protection from Research Risks should make clear to investigators and Institutional Review Boards that the fourth criterion for waiver, that "whenever appropriate, the subjects will be provided with additional pertinent information after participation," is not relevant to research using human biological materials.

NBAC recognizes that if its recommendation that coded samples are identifiable (Recommendation 1c) is adopted, there may be an increase in the number of protocols that require IRB review. If, however, such a protocol is then determined by the IRB to present minimal risk to a subject's rights and welfare, the requirement for consent may be waived if the practicability requirement is revised for this category of research.

NBAC believes that these interpretations and recommended changes in the regulations will allow important research to go forward while still taking into consideration potential harms to

subjects. However, it must be noted that by dropping the requirement that consent must be obtained if practicable, NBAC does so with the expectation that the process and content of informed consent for new studies will be explicit as to the intentions of the subjects regarding the research use of their samples (see Recommendations 11-18).

Finally, investigators still have the option of foregoing IRB review by rendering a sample unidentifiable (unlinked) for all future uses. Doing so would, of course, minimize the possibility that the source might benefit from future discoveries, but this possibility will already be foreclosed, unless there is some reason to believe that at some time in the future it will become possible to recontact the individual even though it is not possible to do so at present. Investigators are encouraged to discuss with IRBs in advance their rationale for removing identifiers from samples if they are concerned that by so doing they are compromising the goals of the research.

Recommendations Specific to the Use of Stored Samples

3. Repositories that are subject to federal regulation should, at a minimum, require that an investigator obtaining samples from their collection provide documentation from the investigator's IRB that research using identifiable samples will be conducted in compliance with applicable federal regulations for the protection of human subjects in research.

4. If the Institutional Review Board determines that there is a need to seek consent the sources of existing, identifiable samples, because, for example, risks have changed, the investigator should submit for the IRBs approval a plan for obtaining consent.

In reviewing this plan the IRB should pay particular attention to the following issues: who will make the contact the contact with the subject and by what means? (e.g., by mail, telephone, or in person); will there be support available to the individual is appropriate in light of the information being conveyed? (for example, regarding predictors of future illness); is the information that will be provided adequate regarding the purpose of the research and the reason the individual's material is proposed for inclusion? What inducements (financial or otherwise) are

being offered for allowing use of the sample, and are such inducements reasonable?

5. For research that requires obtaining informed consent of the subjects, IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research being proposed. Where such documents are inadequate, the IRB should require investigators to submit new consent forms

When reviewing such documents, NBAC recommends that general releases for research executed in conjunction with a clinical or surgical procedure not be presumed to cover all forms of research over an indefinite period of time. Where prior consent documents are found to be inadequate, NBAC recommends that IRBs work with investigators to design the study in a way that permits a waiver of consent or, in the alternative, help investigators to contact subject to obtain a new consent for research.

Recommendations Concerning Research Design

6. Although individuals from whom unidentifiable samples were obtained cannot, by definition, be identified, research using such samples may potentially harm an identified group to which the individuals belong. To the extent possible, investigators should plan their research so as to minimize such harm and seek, where appropriate, input from representatives of the relevant groups regarding study design.

7. For a protocol for research on human biological materials to be approved, the investigator must set forth, and the IRB must approve, a thorough description of the process by which samples are obtained from repositories, and what mechanisms are used to maximize the protection against inadvertent release of confidential information. Such a description should also include any plan by the investigator to access the medical records of the subjects, including protections against inadvertent release of information from the medical record. (See also Recommendations 23 and 24.)

8. In designing protocols, investigators should, to the extent possible, anticipate the need to contact subjects when interim findings suggest the possibility of clinically significant information. IRBs should review these plans for contacting individuals for completeness and for their sensitivity to the problems inherent in the use of preliminary data.

9. **Investigators should provide IRBs with a thorough justification of the research design they will use, including a description of procedures used to minimize risk to the subjects. In studies that may pose risk to others (e.g., groups), IRBs should exercise heightened scrutiny.**

10. **Investigators should provide IRBs with a justification for their decision to use identifiable samples, and whether they intend to seek consent or strip identifiers.**

Recommendations Regarding Informed Consent

Whether obtaining consent to the research use of human biological materials in a research or clinical setting, and whether the consent is new or renewed, efforts should be made to be as explicit as possible about the uses to which the material might be put and whether there is a possibility that such research might be done in such a way that the individual could be identified. Obviously, different conditions will exist for different protocols, in different settings, and among individuals. NBAC notes that the existing debate about the appropriate use of millions of stored specimens endures because of the uncertain and nature of past consents. Investigators and others who collect and stored human biological materials now have the opportunity to correct past inadequacies by obtaining more specific and clearly understood consents. By doing so, the need to render samples unidentifiable may become less frequent, and the need to reconsent minimized. It is with these considerations that NBAC makes the following general recommendations about improving the consent process for the use of human biological materials in research.

The Consent Process

11. Consent to the research use of human biological materials should be obtained separately from consent to clinical procedures.

12. If it is anticipated that the specific research protocol poses a risk to an identified group, this risk should be disclosed in the consent form, and should be a subject of discussion during the consent process.

13. Persons should be offered the opportunity to indicate whether they would like to receive any interim findings. Where subjects indicate their willingness to receive interim findings, the consent form should provide a description of the nature of such findings, i.e., they may not be clinically valid or significant. In addition, a plan must be in place to ensure that the process of consent includes the opportunity for subjects to obtain further advice or assistance.

14. Individuals should be asked if they would object to being contacted in the future for new consent in the event that it is required by the Institutional Review Board.

Consent Forms and Documents

15. When seeking consent in the clinical setting, it should be made clear to the subject that refusal to consent to the research use of biological materials will in no way effect the quality of their clinical care.

16. Persons should be informed of the wide range of possible research uses for human biological materials, including uses that have medical, cultural, political, or economic significance.

17. Consent forms should be developed, as appropriate, to provide potential subjects with the following options:

a) to deny permission for their human biological materials to be used for research purposes;
b) to give consent for the use of their use of samples but only in a manner that severs all links between the research and the person's identity;
c) to give consent for the use of their samples for research purposes that maintains links between the research and the person's identity.

18. Persons should be informed, consistent with existing federal regulations, of the extent to which confidentiality of medical records is maintained (45 CFR 46.(1)(5) and any difficulties associated with maintaining such protections.

Recommendations Regarding Publication and Dissemination of Study Results

19. Plans for disseminating results of research on human biological materials should include provisions to control, reduce, or eliminate the potential for harms to individuals or groups who are related to the sample source (by kinship or other significant associations).

20. When accepting research results for publication, journals should require investigators to indicate whether the research was conducted in compliance with the Federal Policy for the Protection of Human Subjects in Research.

Recommendations Regarding Education and Research Support

21. The National institutes of Health (NIH), professional societies, and health care organizations should continue and expand their efforts to train investigators about the ethical issues and regulations regarding research on human biological materials, and to develop exemplary practices for resolving such issues.

NIH can promote these efforts through the use of such mechanisms as workshops, requirements for training grants and center grants, and funding for research on pertinent topics related to this report. Professional societies can develop training materials on these issues and disseminate information about how research centers have successfully addressed ethical issues regarding research on human biological materials. Special emphasis should be given on developing consent processes that allow patients and research volunteers to make meaningful choices about how biological materials might be used in future research. Continued collaborative efforts between scientists and patient representatives and advocacy groups are likely to be particularly fruitful in strengthening the consent process.

22. Compliance with the recommendations set forth in this report will require additional resources. All research sponsors (government, private sector enterprises, and academic institutions) should work together to make these resources available.

Recommendations Concerning Federal and State Legislation on Medical Record Privacy

23. State and federal legislation concerning medical record privacy should include provisions for legitimate access by researchers. Failure to ensure that researchers retain reasonable access to publicly and privately collected medical record data may unduly burden the progress of science with little additional benefit to individual patients or to society.

[This recommendation allows the Commission to speak to the on-going legislative debate among states and in the Congress over the appropriate degree of protection for medical record and genetic privacy. To the extent that legislators focus their attention exclusively on patient-driven issues relating to confidentiality, employment rights, and access to health insurance, they may inadvertently fail to include legitimate-use provisions in their legislation. As medical research becomes increasingly dependent on clinical data to inform its statistical and informatic analysis, the possibility that this resource may be cut off through overbroad legislation or proprietary impediments is a real concern. Scientists are understandably troubled that biomedical progress may be significantly curtailed if every data-point in an investigation must be paid for, or where whole states have excepted their citizens from legitimate biomedical study.]

24. State and federal legislators are encouraged to enact statutes on medical records research and human biological materials research that are uniform in their approach, unless exceptions are credible and warranted. Departures from uniformity are only desirable where the interests and concerns of one data source imperfectly mirror those of the other. The aim should always be to facilitate a consistent and coherent regulatory regime to govern these interrelated areas of research.

[Lack of uniformity in HBM and medical records regulation may have burdensome or unintended consequences for researchers. Inasmuch as both forms of stored material provide information about their sources that are useful to clinicians and researchers, it makes sense to treat them in a similar fashion generally. For example, an Institutional Review Board could be expected to review analogous studies under similar criteria, whether they involve stored tissue

sampling for genetic indicia of a particular disease or searches through representative medical records for undiagnosed symptoms of that disorder. There may, however, be limits on the degree to which uniformity of oversight is appropriate in any individual statutory or regulatory control. It is more difficult to render medical records truly unidentifiable, for example, and the scope of consent may be materially different for a stored pathological specimen. Legislators should consider carefully the importance of the relative differences between the two materials before departing from a uniform regulatory structure.]

Conclusions

To advance human health it is critically important that human biological materials continue to be available to the biomedical research community. It increasingly will be essential for investigators to collect human biological materials from individuals who are also willing to share important clinical information about themselves. In addition, it is crucial that the more than 282 million samples already in storage remain accessible under appropriate conditions.

The growing availability to third parties of genetic and other medical information about individuals has fueled the current debate about medical privacy and discrimination. As a society we are sensitive to the possibility that the use of information obtained from human biological samples can lead to harms as well as benefits. These concerns require that those who agree to provide their DNA, cells, tissues, or organs for research purposes not be placed at unacceptable risk. Measures to provide appropriate protections for individual privacy and for the confidentiality of clinical and research data are important if significant research is to continue. The recommendations provided in this report are intended to promote the goals of improving health through biomedical research while protecting the rights and welfare of those individuals who contribute to human knowledge through the gift of their biological materials.