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# Chapter 5
# Conclusions and Recommendations

Ethical research pursues its scientific aims without inappropriately compromising the rights and welfare of human subjects. Achieving such a balance is a particular challenge in rapidly advancing fields, such as human genetics. The tantalizing potential for generating major advances can make research activities seem especially important and compelling. At the same time, the novelty of the field can mean that potential harms to subjects are poorly understood and hence might be over- or underestimated. This is particularly true of non-physical setbacks to subjects' interests, which can arise in research on previously collected human biological materials when investigators do not physically interact with the persons whose tissues, cells, or DNA they are studying.

Research sponsors, investigators, and IRBs thus need to exercise great care and sensitivity in applying professional guidelines and government regulations to protect subjects whose biological materials are used in research. Properly interpreted and modestly modified, present federal regulations can protect subjects' rights and interests while at the same time permitting well designed research to go forward using materials already in storage as well as those newly collected by investigators. The interests of subjects and those of researchers are not fundamentally in conflict, for appropriate protection of subjects provides the reassurance needed if individuals are to continue to make their tissue, blood, or DNA available for research. Indeed, public confidence in the ethics and integrity of the research process translates into popular support for research generally.

For most people, the central issue in research using human tissues and cells is the harm that can occur when private information about present or future health status—often previously unknown even to the subject—is revealed. One simple protection for subjects would be to render anonymous all human biological materials used in research. That solution would, however,

seriously curtail many investigations. Instead, the protection of human subjects should take account of the great value for many studies using human biological materials of having access to a certain amount of personal and clinical data about the persons from whom specimens were obtained. That is, the policies and guidelines governing human subjects research ought—under certain circumstances—to permit investigators to have access to sufficient identifying information to enable them to gather necessary data about subjects with informed, voluntary consent. Assuming that adequate protections are present, such information gathering could include on-going collection of medical record data and even requests for subjects to undergo tests to provide additional research information. In some cases, it will even be acceptable for investigators to convey information about research results back to the persons whose samples have been studied. Where identifying information exists, however, a well-developed system of protections must be implemented to ensure that risks are minimized and the interests of sample sources are protected.

Finally, any system of regulation is most likely to achieve its goals if it is as clear and simple as possible. This is especially true here because the federal protections for research subjects depend on investigators identifying the involvement of human subjects in their studies and initiating the institutional review of their protocols. Thus, one reason to modify regulations is to make clearer their description of which protocols are subject to what sorts of prior review; likewise, illustrations and explanations may be useful to clarify how the regulations apply to novel or complicated fields, such as genetic studies using human biological materials.

How well does the existing Federal Policy for the Protection of Human Subjects (the so-called "Common Rule," codified at 45 CFR Part 46) meet these objectives? Specifically, does it provide clear direction to research sponsors, investigators, IRBs, and others regarding how to conduct research using human biological materials in an ethically sound manner? Not entirely. In some cases present regulatory language provides ambiguous guidance for research using human biological material, though the language can be retained if correctly interpreted. For example,

confusion about the intended meaning of terms such as "existing samples," "publicly available," and "minimal risk" has stymied investigators and IRB members.[1] Beyond these ambiguities, certain parts of current regulations do not adequately ensure the ethical use of human biological materials in research, and require some modification. This Chapter provides interpretations of several important concepts and terms in the Common Rule and recommends ways both to strengthen and clarify the regulations and to make their implementation more consistent.

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 25 recommendations in the following areas:

- adequacy and interpretation of existing federal policies for the protection of human subjects
- informed consent
- waiver of consent
- reporting of research results to subjects
- consideration of potential harms to others
- publication and dissemination of study results
- professional education and responsibilities
- federal and state legislation on medical record privacy

[1] See testimony of Mary-Claire King, Ph.D., before NBAC, July 1998, Portland, Oregon.

## Research Activities Beyond Clinical Care

In order to trigger the regulations, an activity must be considered "research," as opposed to a clinical intervention. The current regulations do not apply to purely clinical uses of human biological materials, or to other activities such as quality control procedures or teaching. Rather, they apply to *research* defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (45 CFR 46.102(d)). Examination of stored materials undertaken solely as part of a clinical intervention—as when a pathologist assesses a biopsied specimen to confirm a diagnosis—falls outside the purview of this report. Thus, any study conducted on materials left over from a clinical intervention is subject to the federal research regulations, if the investigator or the investigator's institution is subject to those regulations or if the institution has voluntarily agreed not to supply samples for research without following the federal regulations.[2] As investigators make greater use of human biological materials in a wide range of research, specimen repositories need to understand and adhere to federal regulations.

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

In the context of studies using human biological materials, the lack of clarity regarding several key regulatory terms means that they do not provide the guidance needed by investigators, IRBs, and others. These terms include: "existing and publicly available," "identifiable," "minimal risk," "rights and welfare," and "practicable".

### *"Existing and Publicly Available"*

Under two conditions, research with human biological materials may be exempt from the Common Rule, namely when:

[2]The protections provided by the Common Rule 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; or 2) research conducted at an institution that has provided in its "assurance" with the federal government that all research with human subjects conducted as the institution will be governed by the federal regulations whether or not the research is federally sponsored. In addition, the FDA 2) regulates human subjects research involving an investigational new drug, device, or biologic.

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)).

Furthermore, since current federal regulations define a human subject as a "living individual," research using stored specimens from people who have died would not come with the regulatory protection for human subjects.[3]

Regarding the first exemption (that the samples are existing and publicly available), the Office for Protection from Research Risk (OPRR) interprets the term "existing" to mean any materials that are already collected—that is, "on the shelf"—at the time the research is initiated, whether collected for previous research or nonresearch purposes.[4] "Existing" thus contrasts with samples that are to be collected at a later date as a part of the research protocol in question.

The second criterion in the first exemption—the requirement that samples be "publicly available"—is more problematic. In response to a 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'."[5] Yet this interpretation provides minimal guidance as it leaves unclear which "public" is the relevant (*e.g.*, the general public, the scientific community) and whether "available" is the same as "accessible".

[3] *See* 45 CFR 46.102 (f). 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 below, circumstances may exist in which research on samples of deceased individuals has implications for living relatives; if the findings were attached in some way to these relatives, they might be considered human subjects, which could trigger the federal regulations.

[4] *See, e.g.*, IRB Guidebook, pp. xxx.

[5] Personal communication from OPRR Director, Dr. Gary Ellis, August 25, 1998.

Large repositories, often cited as examples of "public collections" have in place "strict policies to ensure that cultures are distributed only to qualified organizations and researchers with legitimate and justifiable scientific uses for these materials."[6] 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 studies that can reveal biological information about that sample or even health-related information about the person from whom it came. Moreover, some newer DNA databases (*e.g.*, those associated with the federally funded Human Genome Project) are organized 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 requiring that primary human genomic sequence data 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. While the interests of the people who have provided these specimens are indeed best protected by restricting access to these materials to qualified researchers, the fact that such researchers can readily access the specimens does not make them "publicly available" as that term is commonly understood. The reason for exempting publicly available data from the purview of the Common Rule is that people have no expectation of privacy about information that anyone can find and that any harm that may be associated with the disclosure of such information has already occurred and should, in any case, be taken up with those who collected the data and made them public.

It should be noted that the current regulatory policy makes sense in the context for which it was first created—such as a social or behavioral scientist making use of information about

[6] American Type Culture Collection (ATCC), http://www.atcc.org/

people that can be found in directories or newspapers or observed in recordings made of their conduct in public settings. But the exemption would contradict the whole purpose of human subjects protection were it applied to new biological analyses of stored human tissues or cells because the information that may emerge from such a process is not in any genuine sense "existing" much less "publicly available." Furthermore, since the first exemption would encompass data that are identified with individual human subjects, applying that exemption to human specimens in repositories to which researchers have easy access would render moot the second exemption for studies using existing samples, which limits investigators to information that cannot be linked to the subjects.

Thus, while the accessibility of specimens is an important consideration in specifying appropriate levels of protection, more important considerations include: 1) whether the specimens are stored with codes, links, or identifiers; 2) whether identifiable samples (coded or identified) are delivered to investigators for study; 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.[7]

***The "Identifiability" of Samples and the Applicability of the Common Rule***

The second criterion for exemption from the Common Rule (that 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) reflects an underlying premise of the federal regulations, namely that protection is needed when research is conducted with *human subjects*. 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

[7] In reviewing the policies and procedures of several repositories, the Commission found that some require that investigators provide a statement of their research intent and an assurance of compliance with the Common Rule, but it is not clear that this practice is widespread, especially among smaller, more informal tissue collections.

individual, or (b) identifiable private information."[8] 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.[9]

The academic and professional literature on the research use of human biological materials has used a variety of terms to describe the identifiability of research samples. 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.

As noted in Chapter 2, NBAC adopted the following definitions regarding the diverse status of human biological materials, depending on whether they are sitting in storage in a

[8] 45 CFR 46.102(f)(1)&(2).

[9] IRB GUIDEBOOK, pp. 2-9.

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).

**Research samples** are the collections of human biological materials provided to investigators by repositories or collected by investigators in the conduct of research. 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 to investigators from an unidentified collection of human biological specimens.
2. **Unlinked samples**—sometimes termed "anonymized," are those that lack identifiers or code that can link a particular sample to a particular identified specimen or a particular human being. Typically, unlinked samples are sent by repositories from identified human biological specimens to investigators 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, would be extremely difficult for the investigator, the repository, or a third party. They also include those samples already in an investigator's possession whose identifiers have been stripped off by a disinterested party.

3. **Coded samples**—sometimes termed "linked" or "identifiable"—are those supplied by repositories from identified specimens to investigators without personally identifying information (such as a name or Social Security number) but rather, with a code. In such cases, while the repository (or its agent) retains the ability, via the code, to link the research findings derived from the sample by the investigator with the individual, the investigator (or one reading a description of the research findings) would not be able to do so.
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, one could aggregate 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.

**Recommendation 1:**

**Federal regulations governing human subjects research (45 CFR 46) that apply to research involving human biological materials 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 with unidentified samples (i.e., samples taken from unidentified specimens) is not human subjects research and is not regulated by the Common Rule.**

**b. Research conducted with unlinked samples (i.e., samples taken from identified specimens without a link to form a correspondence between a particular sample and a particular specimen) *is* research on human subjects and is regulated by the Common Rule, but is eligible for exemption from IRB review pursuant to 45 CFR 46.101(b)(4).**

**c. Research conducted with coded or identified samples (i.e., samples taken from identified specimens with a link to form a correspondence between the particular sample and the particular specimen) is research on human subjects and regulated by the Common Rule. It is not eligible for exemption unless the specimens or the samples are publicly available as defined by 45 CFR 46.101 (b)(4). Few collections of human biological materials are publicly available, although many are available to qualified researchers at reasonable cost. Therefore, the Office for Protection from Research Risks should make clear in its guidance that in most cases this exemption does not apply to research using human biological materials.**

**d. The Office for Protection from Research Risks should issue appropriate guidance for investigators and IRBs on these definitions or, if deemed necessary, modify the language of the regulations ("the Common Rule").**

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 if not impossible. 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 samples should apply.

Although this seems quite reasonable at first, some controversy remains in the case of samples that have been unlinked 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 unidentified and unlinked 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. (See also Recommendations x and x.)

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

**Recommendation 2:**

**Investigators proposing to use unlinked samples should submit to their IRB (or other review committee designated by their institution) the procedures that will be used to qualify the samples for this category, along with an explanation of the reasons for conducting the research with unlinked rather than coded or identified samples. If the IRB (or other committee) determines that procedures are sufficient to make it extremely difficult for the investigator or a third party to link the results of analyzing a sample with the individual from whose specimen the sample was taken, it may certify the research as not subject to the requirements of the Common Rule. The Office for Protection from Research Risks should issue appropriate guidance for investigators and institutions on these procedures or, if deemed necessary, modify the language of the regulations ("the Common Rule")."**

This recommendation applies only to samples obtained from materials already under the investigator's control. The IRB or reviewing body ought to exercise particular care when the process of unlinking is not carried out by a third party (such as the independent repository that supplied the samples) but rather by the investigator or someone working with or for him or her. What matters is the outcome—that results from analysis of the samples cannot be linked to individual specimens and their sources—rather than the unlinking method used. However, institutions and organizations that participate in research conducted with unlinked samples should institute policies and procedures (e.g., the use of independent third parties to unlink samples) to ensure that the unlinking is genuine.

The requirement of the rationale for unlinking the samples is not connected automatically to a decision by the IRB, but is included so as to allow an IRB to require full IRB review when it determines that the unlinking is unjustified scientifically and/or is being done solely to removed the research from IRB oversight. While unlinking reduces the risk of injury to the specimen-sources, it cannot remove such risk entirely, which is an especially serious consideration if the

unlinking reduces the scientific value of the research (thereby lowering the benefit:risk ratio). Generally, it is NBAC's view that where it is feasible to conduct human biological materials research that accords with the usual protections for research subjects, it is preferable to do so, rather than unlinking the samples to get around those protections.

***Coded or Identified 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. It is important to note, however, that 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 below.

Previous guidelines and reports (see Chapter 3) 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.

**Recommendation 3:**

**Research conducted on human biological materials that are linked to information that could identify the individuals from whom they were obtained, even through a code, is subject to the process of review and approval specified by the Common Rule (45 CFR 46.101(b)(4).**

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 coded or identified samples, even if widely or publicly available, will be subject to the federal policy of protections. Repositories and IRBs share responsibility with investigators to ensure that research is designed and conducted in a manner that appropriately protects human subjects from unnecessary harms.

**Recommendation 4:**

**Before releasing coded and/or identified samples from its collection, a repository**

**should require that the investigator requesting the samples either: a) provide documentation from the investigator's Institutional Review Board that the research will be conducted in compliance with applicable federal regulations; or b) explain in writing why the research is not subject to those regulations.**

**Recommendation 5:**

**When reviewing and approving a protocol for research on human biological materials, Institutional Review Boards should require the investigator to set forth:**
**a) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects;**
**b) a full description of the process by which samples will be obtained;**
**c) any plans to access the medical records of the subjects; and**
**d) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.**

## 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 may 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.

This policy provides significant protection for sources, recognizes that their samples may have been collected without adequate disclosure, and yet provides them the opportunity to participate in research. When the IRB determines existing consent documents to be inadequate and where the existing sample is identifiable, the individual should be contacted, 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 coded or identified) 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]

[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 NBAC, *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, 1998, p.61). NBAC does not regard prospective authorization as valid for enrollment in research, but recognizes its moral value.

### *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.

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.

**Recommendation 6:**

**When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent to clinical procedures.**

**Recommendation 7:**

**The person who obtains informed consent in clinical settings should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.**

**Recommendation 8:**

**When the investigator is conducting research on samples obtained prior to the implementation of these recommendations, general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time. Investigators and Institutional Review Boards should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate, and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research. (See Recommendations xx for waiver of 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 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 through unlinking may become less frequent, and the need to reconsent minimized. It is with these considerations that NBAC makes the following recommendations about improving the consent process for the use of human biological materials in research.

**Recommendation 9:**

**To facilitate collection and storage of human biological materials in the future, consent forms should be developed to provide potential subjects with a sufficient number of options to help them clearly understand the nature of the decision they are about to make. Such options might include, for example:**

**a) To refuse use of their biological material in research;**

**b) To permit only unidentified or unlinked use of their biological material in research;**

**c) To permit coded or identified use of their biological material for one particular study only, with no further contact permitted to ask for permission to do further studies;**

**d) To permit coded or identified use of their biological material for one particular study only, with further contact permitted to ask for permission to do further studies;**

**e) To permit coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies; or**

**f) To permit coded sue of their biological materials for any kind of future study.**

Consent for future research on stored biological materials is difficult because it is impossible to foresee many studies that may be designed in the future. Patients may agree to have their biological materials use in some types of studies, but not others. Consent for future studies is meaningful only if patients appreciate, in so far as is possible, the types of studies that may be carried out. However, attempts to describe in detail future research may be confusing rather than helpful and could be administratively burdensome. NIH and advocacy groups such as the National Action Plan for Breast Cancer have worked on designing "tiered" consent forms that are both informative and practical. Such efforts should be encouraged and continued.

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.

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 him or her.

**Criteria for Waiver of Consent**

When an investigator proposes to do research with coded or identified samples, it is considered research with human subjects. Ordinarily the potential research subject is asked whether he or she agrees to participate. Seeking consent demonstrates respect for the person's entitlement to choose whether to cooperate with the scientific enterprise, and it permits individuals to protect themselves against unwanted or risky invasions of privacy. 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, for example, 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 coded and identified 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."[11] 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.

**Recommendation 10:**

**The federal regulation permitting expedited review for minimal risk research involving materials "that have been collected and will be collected solely for non-research purposes" should be interpreted to mean that all minimal risk research on materials that will be collected solely for non-research purposes is eligible for expedited review.**

The current federal regulations appear to make research on materials that will be collected for clinical purposes or those that will be collected in non-invasive or minimally invasive ways for

[11] Benjamin Freedman, Abraham Fuks, Charles Weijer, "In loco parentis: Minimal Risk as an Ethical Threshold for

research purposes, eligible for expedited review. A grammatical ambiguity, however, appears to make research on existing collections eligible for expedited review only when the existing collection was develop for non-research purposes. NBAC finds that there is no need to distinguish between collections originally created for clinical purposes and those created for research purposes. In both cases, research on the collected materials should be eligible for expedited review if the research presents no more than a minimal risk to the study subjects.

**Recommendation 11:**

> **Institutional Review Boards should operate on the presumption that research on *existing* coded samples is of minimal risk to the human subject if: 1) the study adequately protects the confidentiality of personally identifiable information obtained in the course of research; 2) the study does not involve the release of information to any third party with an interest in the employment or insurability of the human subject; and 3) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.**

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***

Research Upon Children," *The Hastings Center Report*, Vol. 23, No. 2, p.x, March, 1993.

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 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 4 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 4, 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 many studies where it is not necessary that investigators know the identity of sample sources. In these cases, investigators will not have a need to trace sample sources although they might require additional clinical information without identifying the source. Even where investigators need to trace to 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 may threaten their ascriptive identity. Moreover, there remains the possibility that the results of such studies will be used to stigmatize and discriminate against group members (research subjects and non-research subjects alike).

**Recommendation 12:**

**When an Institutional Review Board determines whether a consent waiver "adversely affects the rights and welfare of subjects" it should consider whether the waiver would violate any state or federal statute or customary practice regarding**

**entitlement to privacy. The Institutional Review Board should also consider whether the study examines traits commonly considered to have political, cultural, or economic significance to the study subjects, and whether the study's results might adversely affect the welfare of the subject's community.**

### *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.[12]

Practicable is defined in the ordinary sense as that which "can be done or used," or is "possible in practice" (*Oxford English Reference Dictionary*). In terms of interpreting the regulations 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 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.

**Recommendation 13:**

**If research using existing coded or identified human biological material is determined to present minimal risk, Institutional Review Boards may presume that it would be impracticable to meet the consent requirement (45 CFR 46.116(d)(3)). This interpretation of the regulations applies only to the use of human biological materials collected before the adoption of the recommendations contained in this report (specifically Recommendations xx regarding informed consent). Materials collected after that point must be obtained according to the recommended informed consent process and, therefore, Institutional Review Boards should apply their usual standards for the practicability requirement.**

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

[12.] Personal Communication, Dr. Gary Ellis, Director, OPRR, August 25, 1998.

compelling consideration.

NBAC recognizes that if its recommendation that coded samples should be treated as if identifiable 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 concerning consent).

***Providing Additional Information as Required at 45 CFR 46.116(d)(4)***

In the current regulations, the fourth 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.

**Recommendation 14:**

**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," (45 CFR 46.116(d)(4)) usually does not apply to research using human biological materials.**

This criterion was designed to address the situation in which an IRB has permitted informed consent to be waived or modified with the result that subjects may be aware of interacting with an investigator but still deceived about the true nature of the research, or in which subjects will be unaware of being observed in public settings. Respect for subjects' rights and welfare in such circumstances will usually dictate that they be informed after-the-fact of the research in which they have been involved as "naive" or unwitting subjects, and perhaps offered the opportunity to withdraw their information from the investigator's data. 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 subjects to exclude themselves from a study. Unless someone has "opted out," he or she is 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, his or her sample could not be used in the research protocol.

### *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. A

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. 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.

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 subject's wishes concerning permissible uses of tissue will help to alleviate the need for the investigator to use unidentified or unlinked samples.

Nevertheless, the NBAC recognizes that there will be some situations in which it is scientifically sound or desirable to render samples unidentifiable through unlinking, 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 little or 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 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 unconfirmed 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, contends 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].

**Recommendation 15:**

**Institutional Review Boards should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following obtain:**

**a) the findings are scientifically valid and confirmed;**

**b) the finding indicates a threat to the subject's health; and**

**c) there is readily available a course of action to prevent, avoid, ameliorate, or treat the threat to the subject's health.**

**Recommendation 16:**

**The investigator in his or her research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a**

**subject, as well as a plan for how to manage such a disclosure.**

**Recommendation 17:**

**When research results are disclosed to a subject, appropriate medical advice or referral should be provided.**

**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.[13] NBAC does not assume that because there might be risks to relatives of the sample source, those risks warrant considering those individuals to be human subjects, deserving the protection of informed consent.[14] 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

[13] 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 sample source are likely to be individually identifiable. See DeRenzo, E.G., Biesecker, L.G., and N. Meltzer, " Genetics and the Dead: Implications for Genetics Research with Samples from Deceased Persons," *American Journal of Medical Genetics* 69:332-334, 1997

[14] 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.

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 the Common Rule, 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.[15] 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.

**Recommendation 18:**

**Research using stored human biological materials, even when not potentially harmful to individuals from whom the samples are taken, may be potentially harmful to groups associated with the individual. To the extent such potential harms can be anticipated, investigators should to the extent possible plan their research so as to minimize such harm and should consult, when appropriate, representatives of the relevant groups regarding study design.**

**Recommendation 19:**

**If it is anticipated that a specific research protocol poses a risk to a specific group, this risk should be disclosed during any required consent process.**

[15] 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).

**Publication and Dissemination of Research Results**

Publishing identifiable information in biomedical journals may pose a risk to the privacy and confidentiality of research subjects. Publicly disclosing such information through written description or pedigrees may result in adverse psychosocial effects and, without informed consent of the individual to do so, infringes on the rights of the subject or patient (Botkin et al). Because of the familial nature of information in pedigrees, their publication poses particularly difficult questions regarding consent. Journal editors have an ethical obligation to publish only that human subjects research that they have reason to believe was conducted according to ethical standards set forth in the Common Rule, which includes review by an Institutional Review Board (IRB). Recent studies have reported that ethical standards communicated in journals' instructions to authors vary widely, as does how well authors adhere to such standards.

**Recommendation 20:**

**Plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups.**

**Recommendation 21:**

**When publishing research studies involving human subjects, journals should specify whether the research was conducted in compliance with the requirements of the Common Rule, even if the study was privately funded and exempt from these requirements.**

**Professional Education and Responsibilities**

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.

**Recommendation 22:**

**The National Institutes of Health, 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, conferences, 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.

These discussions 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.

**Recommendation 23:**

**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.**

**Use of Medical Records in Research on Human Biological Materials**

**Recommendation 24:**

**Because research using identifiable human biological materials sometimes requires that investigators have access to information in a patient's medical record, state and federal legislation concerning medical record privacy should include provisions for legitimate access by researchers who have met all applicable review and consent requirements.**

**Recommendation 25:**

**State and federal legislators are encouraged to enact statutes on medical records research that are uniform in their approach and consistent with these recommendations concerning research on human biological materials.**

Differences in the rules governing research on records and human biological materials should be adopted only when required to take account of important differences between the two types of research, while taking into account that the 'information' that can be found by studying cells and tissues differs in important respects from that contained in medical records.

## 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.