Chapter 5
Conclusions and Recommendations

The appropriate protection of human subjects whose biological materials are used in research is as essential as such materials are valuable in advancing scientists' understanding of disease and developing new therapies. The high research value of human biological materials does not override the rights of individuals to protect themselves from possible adverse consequences of the research use of such materials. Potential harms to subjects include, for example, stigmatization, familial conflict or emotional harm, invasion of privacy, inappropriate disclosure of confidential information, and insurance and employment discrimination. NBAC concludes that policies can be developed that protects the rights and interests of human subjects while at the same time permitting research using human biological materials under appropriate circumstances and with suitable safeguards.

Moreover, the appropriate protections must take into account the reality that increasingly the research value of human biological materials is enhanced by the amount of ongoing clinical data (which might be collected over long periods of time) about the person from whom the sample was obtained. That is, it will be important to ensure that the policies that govern the use of human subjects in research make provision for, under certain appropriate circumstances, retaining sufficient identifying information to ensure that important clinical information can go forward 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—it is especially important that the regulations describing which protocols are subject to review are clear, and where it is not that efforts be made to either change the language or offer clear instructions as to the best interpretation of those regulations.

To assess the current system of protections and to determine whether additional guidance or regulation is required, the Commission systematically reviewed the existing Federal Policy for the Protection of Human Subjects (45 CFR, Part 46, or the "Common Rule"),[1] in particular the concepts of identifiable samples, minimal risk and protections of rights and welfare in the 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 employs existing samples or when those samples are collected as part of a research effort. To aid its analysis the Commission also reviewed proposals and guidance prepared and published by scientific, medical, and lay organizations and by other countries regarding the research use of human biological materials.

Two separate but parallel considerations factored into the Commission's analysis of the current federal protections for persons whose biological materials are used in research. The first consideration was the adequacy of the regulatory language. The second was the recognition that the extent to which the language of the Common Rule is adequate may turn on an evaluation of a series of decisions that currently must be made by the investigator, the Institutional Review Board (IRB) administrator or full IRB, and in some cases the repository of human biological materials. These decisions center on whether the activity constitutes research, whether it involves human subjects, whether a protocol is eligible for expedited review, and whether consent of the research subject is required. (See attached charts.)

The Commission concluded that, in some cases, the regulatory language is adequate given a specific interpretation, but if interpreted broadly might not be sufficiently protective, thereby

1. The protections provided by federal regulations currently apply only to: 1) research conducted or funded by one of the 16 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.

requiring additional clarification and education efforts. There are numerous ambiguities in the language of the Common Rule; for example, it refers to undefined terms such as "existing samples," "publicly available," "minimal risk," and "private identifiable information." Confusion about the intended meaning of these terms has stymied investigators and IRB members who testified before the Commission and, indeed, members of the Commission as well.

In other cases the Commission concluded that the regulations themselves are not adequate to ensure the ethical use of human biological materials in research, thereby requiring 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 appropriate research goes forward with the necessary protection of human subjects. In this final chapter, the Commission 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 CONSTITUTE RESEARCH

One of the first issues to be addressed when assessing the level of review required to proceed with the use of human biological materials is to determine which activities constitute "research." Although the Commission chose to address only the use of human biological materials in research, the term "research" requires some clarification. The current regulations and NBAC's recommendations do not apply to purely clinical uses of such materials. Rather, the regulations and the Commission's recommendations apply to research defined as "a systematic investigation designed to develop or contribute to generalizable knowledge" (46.102(d)). If work on stored materials is done solely as part of a clinical intervention, as might be the case in a pathology laboratory, then the federal regulations, and NBAC's recommendations, do not apply. If, however, 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.

In general, work that has both a clinical *and* a research component is covered by the federal regulations and by NBAC's recommendations. Any research done 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 clinical care institutions that anticipate research involving stored human biological materials collected primarily for clinical purposes.

CURRENT CRITERIA FOR EXEMPTION FROM THE FEDERAL POLICY FOR PROTECTION OF HUMAN SUBJECTS

The federal regulations state that 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)).

The Commission 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. As previously noted, 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]

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

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. Generally speaking, the Commission interprets (as does the federal Office for Protection from Research Risks, or OPRR) 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 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 the Commission found to be more problematic. A requested OPRR clarification of the meaning of "publicly available" defined it 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] 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 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

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involved, triggering regulatory oversight.

3. IRB Guidebook

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

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

wanting to investigate the basic structure or function of DNA. Thus, although collections might be widely available to the research community, it appears that they are infrequently available to any member of the public.

Possibly more important than who has access to the samples is: 1) whether the samples are stored with or without identifiers; 2) whether identifiable samples are delivered to investigators seeking access; and 3) whether the respositories require any assurance that the research will be conducted in a manner that will protect the rights and interests of the sample sources. In its review of 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 (45 CFR Part 46),[6] but it is not clear that this practice is widespread, especially among smaller, more informal collections.

NBAC identified a third concern with the exemption criteria. The second criterion states that the research is exempt if "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))." The Commission concluded that the policy would better protect human subjects, while still preserving the scientific value of the samples, if someone other than the investigator coded the samples or rendered them unidentifiable, for example the repository or an encryption service.

In sum, NBAC concluded that the existing criteria for exemption from the federal requirements of IRB review and informed consent are not sufficiently protective of human subjects for the reasons described above.

Recommendation 1: Research conducted on human biological samples that are existing and publicly available is exempt from regulatory oversight only when the samples are either unidentifiable, or rendered unidentifiable by someone other than the investigator. Coded samples are considered identifiable.

Recommendation 2: Repositories should require that investigators obtaining samples from their collections provide documentation that research using identifiable samples will be conducted in compliance with the federal regulations for the protection of human subjects in research.

The Commission does not believe that this change in criteria for exemption would 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 changes will ensure that research conducted on identifiable samples, even if widely or publicly available, will be subject to the federal policy of protections.

IDENTIFIABILITY OF SAMPLES

According to the federal regulations, a key consideration in deciding whether research is subject to IRB review and informed consent requirements is whether the identity of the sample source can be determined, either directly or through identifiers linked to the subjects, from the investigator's records. As previously noted, 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. Within the regulatory framework, the determination of identifiability is the key to determining whether, in fact, the proposed research activity involves a human subject. One reason identifiability is a key criterion is that 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. In addition, when samples are identifiable

6. Coriell Institute for Medical Research.

the information obtained from them may be misused or misdirected, resulting in harms to the human subject, such as discrimination or stigma.

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

The Commission has determined that human biological samples fall into the following four categories:

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

2. Unlinked samples—sometimes termed "anonymized"—are those supplied by repositories from identified human biological materials 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 impossible for the investigator, the repository, or a third party.

3. Coded samples—sometimes termed "linked" or "identifiable"—are those supplied by repositories from identified materials 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 materials 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.

7. IRB Guidebook.

4. Identified samples are those supplied by repositories from identified materials 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 the regulations, the Commission groups these further 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 the investigator cannot ascertain the identity of the person from whom the sample originated.

Several repositories keep a record of the sources from whom the samples came so that the repository can track that a sample was sent forward. Such samples are numbered in such a way that even the repository cannot link the sample to its source. Such 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 sample. 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 feasible 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 anonymous (not merely "anonymized") 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 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 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 stripping identifiers the investigator eliminates the possibility to obtain a consent that might have been given had reasonable efforts been made to find the source. 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. In addition, 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.

If one were to embrace these concerns as valid and substantial, one possible recommendation would be to restrict use of existing, unidentifiable samples because consent cannot be obtained. NBAC believes this to be an untenable conclusion.

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 pose harms for 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 advanced consultation with relevant groups, alterations in research design, or greater care in the manner in which research results are reported.[8]

In addition, given the importance of society's interest in advancing medical progress, a policy that severely restricted research access to these unidentifiable samples would severely hamper research and would waste a valuable research resource.

Recommendation 3: In most cases the Common Rule provides adequate protection of the interests relevant to the use of unidentifiable samples (which include both unidentified and unlinked samples). Since the individuals from whom such samples were originally obtained cannot, by definition, be identified no special restrictions should apply to research with such samples. Researchers should be mindful, however, that some types of research on unidentifiable samples, while posing no potential for harm to the sample source, might pose potential harms to groups of individuals, and should therefore design research that minimizes such risks.

Identifiable Samples

Within the "identifiable" category are two subcategories: 1) coded or encrypted samples;

8 This issue is addressed further below under "Considerations of Potential Harms to Others."

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 tissue bank or 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 material sent to the investigator. Thus, the code could be broken if necessary. 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. (Note: The ease of identifying the source is part of the calculus in determining the level of risk posed by the research, to be 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 was apparent from NBAC's discussions and review of the literature 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.

Recommendation 4: The official interpretation of present federal regulations, and the language of the regulations themselves, should be revised to make clear that research on human biological materials that are linked, even through a code, to identifying information about their source constitutes research on a human subject and is governed by federal regulations.

ISSUES REGARDING MINIMAL RISK AND RIGHTS AND WELFARE

Determining the risk and effects 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. The first two criteria that must be evaluated in considering the need for consent are:

1) whether the research involves no more than minimal risk to the subjects; and

2) if the waiver or alteration of consent will adversely affect the rights and welfare of the subjects (45 C.F.R. Sec. 46.116(d)).

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" (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 raise legitimate questions about the applicability of the baselines that the regulations provide 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 baseline 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 and uses of 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.."

The Commission does not accept this analysis of "minimal risk." 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; instead, 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 here is that the purpose of assessing whether risk is "minimal" is to help determine whether it is permissible to lower the level of protections afforded subjects. While the letter 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."[9] 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" (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 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

9. 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.

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 in their interest 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 will 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).

CONSENT REQUIREMENTS

The adequacy of the requirement of informed consent, or other protections such as IRB review, can be evaluated in terms of whether or not they achieve an appropriate balance of interests. In considering the conditions for which informed consent should be required for the research use of human biological materials, the Commission 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. 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 C.F.R. Sec. 46.116(d), are met. The first two criteria, concerning minimal risk and effects on rights and welfare of the subjects have already been discussed. The remaining two criteria, that the research "could not be practicably carried out without the waiver or alteration," and that, "whenever appropriate, the subjects will be provided with additional pertinent information after participation," are discussed below.

"Practicability" of Obtaining Informed Consent

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.[10]

In many cases, it will be prohibitively costly, extremely difficult, and needlessly intrusive to re-contact individuals from whom biological samples have previously been obtained for the purpose of either clarifying the previous consent they provided or obtaining a new consent for research use of the sample. To require that every conceivable effort be made to re-contact every source, without regard to costs, seems unreasonable and unwarranted in cases where an IRB has already determined that a protocol is minimal risk and has no adverse consequences for the subject's rights and welfare.

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 consent requirements should rest on the principles of protection of rights and welfare and avoidance of harm, not on the ability to obtain consent.

Recommendation 5: If research using identifiable existing human biological materials is determined to be of minimal risk, with no adverse consequences for the subject's rights and welfare, the consent requirement should be waived without meeting the practicability requirement. This requires a change in the federal regulations. Protocols that do not meet these proposed requirements for waiver of consent would continue to be subject to the practicability requirement.

The Commission recognizes that if its recommendation that coded samples are identifiable (see Recommendation 1) is followed, there will be an increase in the number of protocols required

to undergo IRB review. If, however, such a protocol is then determined by the IRB to be minimal risk and without adverse impact on rights and welfare, the requirement for consent could be waived. The Commission believes that this regulatory change would allow important research to go forward while still taking into consideration potential harms to subjects. Moreover, it is NBAC's perception that most research using stored human biological materials is likely to be of minimal risk, with no consequences for rights and welfare, so that a substantial number of protocols will likely fit into this category of review. For those protocols determined to be of greater than minimal risk or with adverse consequences for the subject's rights and welfare, the consent requirement could not be waived.

Investigators still have the option of foregoing IRB review by rendering a sample unidentifiable (unlinked) for all future uses. Doing so would of course eliminate any 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 re-contact the individual even though it is not possible to do so at present.

Informing Individuals about Research

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., 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 convey some information to the subjects. Such a communication might describe the status of the research project and inform

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

them that their samples will be used or were used in the research. Such a requirement might only be appropriate if general 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 after the research is conducted. If the information is conveyed to the subject before the research is done, allowing the individual to "opt out" of the research provides an additional increment of protection of the rights and welfare of individuals.

"Opt Out" as an Additional Measure of Protection

As described above, NBAC recommends that the consent requirement be waived after a protocol meets the first two criteria: minimal risk and no adverse affects on the subject's rights and welfare. If after such a waiver is granted, the investigator or the 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 that can be taken is 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.

Recommendation 6: As an additional measure of protection in studies for which the consent requirement has been waived, particularly research that some individuals might find objectionable on moral or other grounds, the investigator, institution, and the IRB should consider the option of making a good faith effort to contact subjects to allow them to "opt out" of the research. Such an approach, however, should not be considered equivalent to consent.

Informed Consent Requirements for the Use of Existing Samples

Samples 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 do not 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 tissue must be respected. Where consent documents exist, they may indicate whether individuals wanted their sample to be used in future research.

Recommendation 7: When research is conducted using existing identifiable samples, and if requirements to seek informed consent have not been waived, IRBs should evaluate any existing consent documents for applicability. Where the IRB determines that the proposed research was agreed to at the time the sample was obtained, there is no need for further consent. The IRB still may choose to require that the investigator inform the sources about the new project to provide general news about the results and/or the choice of dissenting from participation in the 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 research of the type in question? If the source consented to the sample being used in unspecified future studies, is that consent sufficient 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 it may be appropriate to judge consent to unspecified future uses as sufficient consent to proposed research. For example, as stated by Clayton, et al., "Even 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 of the research 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 cutting them off—without their consent—from the possibly life-saving benefits of future research would be as follows. Where an existing sample is identifiable, and the IRB judges existing consent documents to be inadequate, the individual can be offered the option of giving consent to the specific proposed protocol, and further offered the option of deciding how the sample may be used in the future.

Recommendation 8: When an IRB determines that the requirement of informed consent cannot be waived and that any existing consent document is insufficient to permit an existing sample to be used in the study, subjects may be offered the following options:

1) giving authorization for future research use of the sample, with a written assurance

that appropriate measures will be taken to ensure confidentiality regarding the sample (appropriate measures might, for example, include the use of certificates of confidentiality). This option should include a statement that the individual's identity shall not be used in recording or publishing results;

2) consenting to the specific proposed protocol;

3) having his or her sample rendered unidentifiable for all future research uses; or

4) stating that the sample cannot be used for any future research uses.

As in the case with research proposing to obtain new samples, individuals should be provided with information to assist them in thinking through these complex decisions. 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 (45CFR46.116[a]). The following points should be highlighted in the consent process:

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 tissue.
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 a special 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.

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.

Recommendation 9: Where particularly sensitive research is proposed and where the source of an existing identifiable sample has given permission for his or her sample to be used in unspecified future research, the individual should be given the opportunity to dissent from participation in such research.

Re-contacting Individuals

The Commission has identified at least five situations in the course of research when individuals may need to be re-contacted:

- to inform individuals about a study in which their sample will be used;
- to inform individuals that their sample will be used in a specific research study unless they contact the investigators to object to such use ("opt out");
- to notify individuals that the nature of the research using their sample has changed;
- to obtain consent for a new protocol; or
- to divulge results obtained in the course of research.

In each of these cases, 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 re-contact 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 find out, after the fact, that his or her material had been used in an experiment, unbeknownst to the subject.

Recommendation 10: Investigators and IRBs should determine whether there is a need to re-contact subjects and, where such need exists, IRBs should review the plan to re-contact the individual. In reviewing this plan the IRB should pay particular attention to the following issues: who will make the contact and by what means, e.g., by mail, telephone, or in person; whether the support that will be available to the individual is appropriate in light of the information being conveyed (for example, regarding predictors of future illness); the adequacy of the information that will be provided about the purpose of the research and the reason the individual's material is proposed for inclusion; and any incentives offered for allowing use of the sample.

RENDERING EXISTING IDENTIFIABLE SAMPLES UNIDENTIFIABLE

Some have recommended that for research using existing identifiable samples, in which it is impracticable or problematic to gain express informed consent for a specific use of the sample, an ethically acceptable option is to render the samples unidentifiable in order to use them for research purposes. The rationale for this 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. Given the cost of a policy of requiring specific consent for all future uses, this proposal might be desirable for some investigators. One unfortunate consequence of this approach, however, is that 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.

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 truly unidentifiable by anyone. 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. 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.

The Commission 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 C.F.R. Sec. 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.

Recommendation 11: 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. In cases where research is conducted on samples rendered unidentifiable, the investigator alone should not be responsible for stripping identifiers. Preferably the repository should do so before sending the materials forward to the investigator (see also Recommendation 1).

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 Commission 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, the Commission 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 gone. Furthermore, contacting individuals might be disruptive and even unwanted by the sample source. With these considerations in mind, NBAC concludes that it is ethically acceptable to render samples unidentifiable without the source's consent. In arriving at this conclusion, the Commission also considered input it received during its mini-hearings, 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..

COLLECTION OF HUMAN BIOLOGICAL MATERIALS IN THE FUTURE

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 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.

Recommendation 12: NBAC recommends that steps be taken to improve the informed consent process when samples are donated in the course of clinical care. Some of the problems with informed consent in this setting can be alleviated by separating consent for future research use of the individual's tissue from decisions about the clinical procedure. One way this can be accomplished is by using a separate consent form, or clearly distinct section of the clinical consent form, that deals exclusively with the possible research use of the tissue. Individuals should be asked to provide separate consent for such uses.

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 work 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 re-contact efforts.

REPORTING RESULTS TO RESEARCH SUBJECTS

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

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 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, for persons other than the subject can also suffer as a consequence of the research.

Recommendation 13: Investigators conducting research on human biological samples should consider potential harms to persons who are not the (identifiable) sources of the samples, minimize these risks in the design and implementation of a protocol where feasible, and consider the implications of publishing research results where such results may identify individuals at risk of harm who are not the subjects, per se, of the research (e.g., pedigree studies).

Recommendation 14: Scientific and medical organizations should develop guidance for their membership for consideration of potential harms to others in research conducted on human biological materials and develop strategies for minimizing harm through innovative research design, methods, and publication practices.

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. Towards this end, DHHS has recommended to the President the establishment of a Task Force on Participatory Research. NBAC supports this recommendation and encourages further efforts to develop strategies for protecting persons who may be affected by research but

who are not currently defined as "human subjects."

It also seems appropriate to highlight how these issues ought to be debated among researchers and their professional organizations. For example, are there sound objectives in public health policy that outweigh the potential for genetic studies of this sort to foster divisiveness and discrimination and to reinforce racist use of genetic information? 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

A subset of the risks to others is risk to first-degree relatives, or next-of- kin. The need for such consideration 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 to be human subjects, deserving the protection of informed consent.[12] In fact, the Commission 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

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 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.

considered, the Commission 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.

Different 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.

PUBLIC AND PROFESSIONAL EDUCATION AND CONDUCT

Education of the public including but not limited 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 is an essential part of effective public policy on the use of human biological materials for research. 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

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).

should fall on researchers to elicit from prospective contributors, both individual and communal, the values and meaning they attach to the requested samples.

Recommendation 15: OPRR should begin an education program for the research community, repositories, and IRBs to ensure that the regulations are clearly understood and followed, including NBAC's guidance on the meaning of key terms that IRBs must interpret as they decide whether to expedite review or waive consent, such as "minimal risk," "impractical to seek consent," and "affecting subjects' rights and welfare."

Recommendation 16: When submitting research for publication, investigators should be required to indicate to journal editors whether the samples used in the research were from identifiable human subjects, whether (and to what extent) informed consent was obtained, and whether prior approval by an IRB was obtained.

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 donate 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 guidance provided in this report is 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.