Chapter 5
Conclusions and Recommendations

Protecting the human subjects whose biological materials are used in research is vital. The National Bioethics Advisory Commission's (NBAC) deliberations on the use of human biological materials revealed that such materials are immensely valuable to advance our understanding of disease and to develop new therapies. NBAC concludes as well that the rights and interests of human subjects can be protected at the same time as research using such materials is permitted under circumstances described in our recommendations. Furthermore, the Commission recognizes that increasingly the research value of human biological materials is enhanced by the amount of, and at times ongoing accumulation of, clinical data about the person from whom the sample was obtained. That is, it will be important to ensure that the policies which govern the use of human subjects in research permit, under appropriate circumstances, the retention of identifiers, perhaps in a coded manner, to ensure that important clinical information can go forward to the investigator and in some cases, back to the research subject. This aspiration requires that there be a rigorous system of protections to ensure that risks are minimized and the sample source's interests are protected.

To assess the current system of protections and determine whether additional guidance or regulation is required, the Commission 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 minimal risk and protections of rights and welfare in the context of research using human biological materials, and the nature of informed consent when research employs existing samples versus those collected as part of the research effort. The Commission recognized that the extent to which the Common Rule is adequate is determined through ones 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 a human biological materials repository.

Finally, NBAC 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 several conclusions regarding its interpretation of the federal regulations and makes recommendations for how to strengthen, clarify, and make more consistent the implementation of protections of individuals who contribute biological specimens to the biomedical research endeavor.

[1] The federal regulatory protections currently only apply to: 1) research supported by funding from one of the 16 federal agencies who have agreed to be subject to the Common Rule; 2) research on an investigational new drug, device or biologic subject to FDA rules; or 3) research conducted at an institution that has executed an assurance with the Federal Government stating that even research not otherwise covered by the regulations will nonetheless be governed by them.

ADEQUACY OF THE COMMON RULE FOR RESEARCH USING HUMAN BIOLOGICAL MATERIALS

For research activities covered by the Common Rule, NBAC concludes that the existing regulations generally provide for adequate protections against harms to individual research subjects that could result from the research use of human biological materials and new regulations per se are not required. However, additional clarification of and educational efforts regarding the existing regulations are needed.

Despite the adequacy of the existing regulatory framework there are numerous ambiguities in the language of the Common Rule requiring clarification. For example, the terms "existing," "minimal risk," "human subject," and "private identifiable information" are sufficiently ambiguous to have stymied several investigators and IRB members who testified before the Commission. This confusion may contribute to uncertainty about the following important considerations in the federal regulations:

- When is certain research using human biological materials exempt from IRB review?
- If the research is not exempt, what level of IRB review is required?
- When is informed consent of the research subject required to conduct non-exempt research?

Each of these questions was addressed by NBAC in its deliberations. The remainder of this chapter works through the Commission's conclusions and recommendations as it followed the flow of decisions that must be made in determining the level of protections required. (The reader is referred to Charts a, x, y, and z, as a guide for these discussions.)

Activities that Constitute Research

One of the first issues to be addressed when assessing the level of review required in order to proceed with the use of human biological materials is to determine that the activity, in fact, constitutes "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 interventions, even if they are experimental in nature. 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 do not apply.

Work that has both a clinical and a research component, however, is covered by the federal regulations. Any research done with samples left over from a clinical intervention 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 that have been collected primarily for clinical purposes.

Criteria for Exemption from the Federal Requirements of IRB Review and Informed Consent

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) samples, that is, when the research uses samples from those who are no longer living. As discussed later, the regulations define a human subject as a "living individual" (45 CFR 46.102 (f)).

The subtle meaning of some of the regulatory language pertaining to exemption may not be clear. Generally speaking, the Commission interprets (as does the Office for Protection from Research Risks, or OPRR) the term "existing" to mean any samples that are already collected, that is, "on the shelf" at the time the research is proposed[2]. According to OPRR this includes data or specimens already collected in research and nonresearch activities. This contrasts with samples that are to be collected as a part of the research protocol. Because most tissue samples are not publicly available[3] most research will not be exempt on that condition alone. Therefore, the next issue to address is whether the identity of the sample source can be determined.

According to the regulations, the answer to this question is the key to determining whether, in fact, the research activity involves a human subject and therefore, whether some form of IRB review is required.

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[2] IRB Guidebook

[3] OPRR responded to an NBAC inquiry 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'." Personal communication from Dr. Gary Ellis, August 25, 1998.

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[4].

The Commission has determined that for purposes of this report, human biological samples fall into two categories: 1) ***identifiable samples*** are those for which the source can be identified (more or less), which means the sample can be connected, or linked, to the person from whom it came; and 2) ***unidentifiable samples*** are those for which the source cannot be identified at all. We refer to the former as 'more or less' because the information content of research samples vary, from a very few data points that, nevertheless, could allow one (perhaps with some difficulty) to link the sample to a person, to an exhaustive number of data points allowing very easy identification of the person from whom the sample was obtained.

Identifiable samples retain the potential for contact of the subject by the investigator or a third party. For example, an investigator might want to contact an individual to gather more

[4] IRB Guidebook

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.

Unidentifiable Samples

Truly unidentifiable samples (both unidentified and unlinked) have no linking data and therefore no one has the ability to determine the identity of the source of the specimen. When research uses unidentifiable samples, contact is impossible. Thus, according to the federal regulations, research using existing samples of this type is exempt from IRB review. The discerning 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 diminishes 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, it is not as uncontroversial as it first appears. Some might consider it insufficient to conclude that just because consent *cannot* be obtained does not mean it *ought* not be obtained. Nor, one might argue, is it correct to assume that because the sources cannot be identified they cannot be harmed. There are some interests of the sample sources that may be harmed even if the sources are not 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 unidentifiable samples. In addition, one could envision that individuals might have an interest in avoiding uses of their tissue that they regard as impermissible or objectionable on moral grounds.

If one were to embrace these concerns as valid and substantial, then a logical conclusion would be to restrict use of existing, nonidentifiable samples because consent cannot be obtained. NBAC believes this to be an untenable conclusion for a variety of reasons.

First, because the samples are not linkable by anyone to individuals, some of the most important interests that weigh in favor of restricted access do not apply. That is, if the individual cannot be identified, then there is 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 nonidentifiable stored samples is significantly weakened.

Second, given the importance of society's interest in advancing medical progress, to restrict research access to these samples would have devastating consequences for the research enterprise and would be a waste of a valuable research resource.

NBAC agrees with current federal policy on genuinely unidentifiable samples. Because the individuals who originally provided the samples cannot be identified, informed

consent would be impossible to obtain. But since the potential for harm to those same individuals effectively disappears, informed consent is not necessary and no special restrictions should apply to research with such samples.

Identifiable Samples

Within the "identifiable" category are two subcategories: 1) coded or encrypted samples; and 2) directly identified samples (i.e., where the investigator can identify the donor). 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 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. In other cases, the repository might retain enough of a linkage that it knows if, in fact, an individual sample was one of a batch of samples sent forward to the laboratory, but has no way of definitively linking a specific sample in its collection to a specific sample in the batch that was sent to the investigator. Although the ease of identifying the source is greatly curbed 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 level of risk, 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 uniqueness of the clinical information that accompanies the material when it is delivered from the repository.

NBAC concludes 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 subject to federal regulations. Guidelines to IRBs should make this very clear.

Criteria for Expedited Review

Once it is determined that research using human biological materials is not exempt from the regulations because it involves the use of samples that can be linked to the source, the next

consideration relates to whether the research is eligible for expedited IRB review or IRB review that grants a waiver of consent. In short, expedited review is carried out by the IRB chair or one or more experienced reviewers, designated by the chair from among members of the IRB, who review the research and approve it or refer it to the IRB for full IRB discussion. To qualify for expedited review, an activity must: (1) involve no more than minimal risk and be found on the list published at Federal Register 46: 8392; Jan. 26, 1981; or (2) be a minor change in previously approved research during the period of one year or less for which approval was authorized by the IRB. Expedited review, although conducted by as few as one IRB member, and done so in the time period between convened IRB meetings, is nonetheless a full review with regard to all clauses of the regulations. Therefore, the totality of the regulations (including requirement for informed consent) provides for the rights and welfare of the subjects in the case of expedited review.

Thus, for research on human biological materials, a key question concerning eligibility for expedited IRB review will be whether the research poses more than a minimal risk to the subject. Consideration of risk is also a significant criterion for determining the need to obtain consent (discussed later). This assessment will depend upon the type of research being conducted, its psychosocial and clinical significance for the subject, and the likelihood that the finding of the research will be transmitted to the subject, or to anyone else who could associate the findings with the subject.

ISSUES REGARDING 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 examinations or tests" (46.102 (i)). "Minimal risk" thus concerns relative risk rather than absolute risk. That is, 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 significant relative to risks which persons "ordinarily" face outside of the research context.

One can plausibly argue that in most instances the principal risks associated with research involving human biological materials are not greater than the risks "ordinarily encountered in daily life." 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 generally face the risk that diagnostic, predictive, and other forms of information about them contained in their medical records will be

accessed and used in a harmful manner. There is no reason to think that research on biological samples typically poses greater risks of harm than those faced in connection with medical records. Indeed, research on biological samples probably poses lesser risks, since the sources of "identifiable" samples—unlike the subjects of medical records—are often unknown and may be difficult to trace. Hence, it appears that most research on biological samples must be deemed "minimal risk."

There are, however, some studies that pose risks that may be greater than minimal. Controversial studies requiring "special scrutiny" (see below), such as those that involve behavioral genetics or that make explicit comparisons between ethnic or racial groups, will probably offend research subjects and threaten their ascriptive identity to a degree greater than that which persons generally encounter in everyday life. (*A possible recommendation here might be to state that all "special scrutiny" studies—as defined elsewhere in the report—should be regarded as greater than minimal risk)*

The idea that most research on biological samples can be characterized as minimal risk may not be easy to accept. For the analysis that leads to this conclusion is one in which the actual risks of harm resulting from the research are not considered at all. In principle, it is possible for research risks to be very high but nevertheless "minimal." As long as the risks of daily life are

greater than or equal to the research risks, the actual level of the research risk may be very minor or quite substantial.

Given that protocols that involve no more than minimal risk are eligible for expedited review and satisfy one of the conditions necessary for a waiver of consent, there are grounds for concern about the relativity of minimal risk. It seems problematic that a finding of minimal risk should play a role in the streamlining of the review and consent process when this finding is consistent with great risks of harm to the subject. In the case of waiver of consent, subjects are protected by, among other things, the additional requirement that the waiver must "not adversely affect the rights and welfare of the subjects" (46.116 (2)(d)(2)). In any instance of research on samples where "minimal risks" are substantial, a waiver of consent should not be permitted because it would improperly deny the important interest persons have in choosing whether to assume significant risks to their well being. With respect to expedited review, however, there is no such additional requirement to ensure the protection of full review when minimal risks are great.

(*The Commission may wish to recommend here that in order for a protocol to qualify for expedited review it must not adversely affect the rights and welfare of subjects)*

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 it is a profound mistake to proceed as if some version of such a requirement *by itself* can provide protection for all the legitimate interests at stake in the practice of gathering and using biological samples. Instead, what is needed is an approach in which informed consent plays an important but not exclusive role in safeguarding both human subjects and research interests. Moreover, attempting to safeguard against all possible harms to those who provide samples by an overly elaborate informed consent requirement is not only unlikely to succeed, but also would be unconscionably costly and an excessive constraint on socially valuable scientific research.

As stated in the federal regulations, all human subjects research generally requires 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:

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

2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

3) the research could not be practicably carried out without the waiver or alteration; and

4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Preceding text has already presented NBAC's discussion of the issues relevant to considering the level of risk. The remaining conditions, affects on rights and welfare, practicability, and provision of pertinent information to subjects, are discussed below.

Rights and Welfare

There are two basic ways in which a waiver of consent can adversely affect the rights and welfare of subjects: (1) The subject may be improperly denied the opportunity to choose whether to assume the risks which 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 new collection of biological samples would violate 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 a waiver of consent for the use of existing samples, the interests at stake are different. In this context, it is principally the social and psychological harms delineated in Chapter 3 that are at issue. A subject's 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, which 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 access information about the source? (Privacy/confidentiality laws may be relevant here, as is the integrity of investigators and their institutional confidentiality mechanisms).

(4) If non-investigators access 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 largely speculative at present. The question thus arises as to how to assess rights and welfare under conditions of uncertainty about the probability of their being adversely affected. The regulations place the burden on IRBs to document that research will not adversely affect the rights and welfare of subjects. Where the sample source is very difficult to trace, and

where investigators have demonstrated that mechanisms are in place to ensure confidentiality for the subject, an IRB might reasonably find that the probability of harm is low enough to satisfy the rights and welfare requirement. In most other cases, however, the present lack of data on psychosocial harms resulting from research on samples renders it difficult to document that a subject's rights and welfare will not be adversely affected. Evidence supporting such a finding may emerge in the future, especially if effective anti-discrimination and privacy laws are passed. But, for the moment, most research on biological samples does not satisfy the rights and welfare condition for waiver of consent.

"Practicability" of Obtaining Informed Consent

When considering a waiver of the informed consent requirement for research use of human biological materials, the investigator 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.[5]

In many cases, it will either be prohibitively costly or extremely difficult to re-contact individuals from whom biological samples have previously been obtained for the purpose of either

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

clarifying the previous consent they provided or obtaining a new consent for research use of the sample. These potential constraints contain more than a grain of truth: to require that every possible effort be made to re-contact every source, without regard to costs, seems unreasonable. However, this is not to say that reasonable efforts to re-contact sources should not be made and that reasonable efforts may entail significant costs. It is not a matter of either spending without limit until every source is re-contacted or making no effort to re-contact them. A third alternative is to require a reasonable (or "good faith") effort to re-contact sources. More is said later about the nature of the recontact effort.

The point of attempting to contact identifiable sources of existing samples to obtain or clarify consent is to respond to a potential dignitary harm that might have occurred, namely, a failure to disclose to the source that a sample will be used for a wide range of purposes unrelated to the medical intervention or particular research project in which the sample was collected. The original failure to disclose such purposes may have been because such research uses were not anticipated at the time the sample was collected, or, in some cases, could be a result of not treating persons respectfully. Regardless of the reason for lack of adequate consent, it is unreasonable to conclude that there is no limit to the costs that ought to be borne to redress this deficiency. Instead, a requirement of making "reasonable" or "good faith" efforts to contact sample sources will generally be an adequate recognition of the fact that in many cases samples were collected in a manner that has subsequently failed to meet the conditions of informed

consent. What counts as reasonable efforts would have to be made clear so that compliance with this requirement could be effectively monitored, and in such a way as to provide adequate assurance that those charged with the research actually made meaningful efforts to contact sources. It is important to remember that the "reasonableness" of the contact effort has to be viewed in light of the level of risk of the study (i.e., above or below minimal risk) and the assessment of the potential for adverse affects on the rights and welfare of the subject.

If reasonable efforts to contact the source fail, and all of the other conditions for waiver of informed consent have not been satisfied, then in general the appropriate course of action will be to render the sample unidentifiable in 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.

If reasonable efforts have been made to contact the subject to obtain informed consent, and all the other conditions for waiver of informed consent have been satisfied, NBAC recommends, as stated in the regulations, that the IRB may waive consent.

[Please note: NBAC might want to be more specific about the criteria one should use in determining practicability. Cost is one measure, difficulty of locating subjects is another.

What about threats to health (individual and public) if the research cannot go forward? This argument was used in the testing of investigational new drugs on combat personnel during the Gulf War. There is also the research design issue: if it is necessary to recontact a whole population for study to obtain explicit consent, might it bias the resulting available study population? Needs discussion]

Informing Individuals about Research

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 important 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

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 reconsent 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 loosely 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, the source's consent will generally be required for research using identifiable samples where the risk is greater than minimal, or where there are threats to the rights and welfare of the subject. There may be cases, however, for which the adequacy or status of the existing consent is not clear, yet the risk is minimal, so the IRB decides that consent can be a waived.

As an extra 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, NBAC recommends that the IRB have the option of requiring that the investigator contact subjects to allow them to "opt out" of the research. Such an approach, however, should not be considered a proxy or surrogate for 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. In some instances, individuals make informed choices about how their sample should be used subsequent to its original research or clinical use (that is, given the option they might decide that new and different uses of the tissue are or are not acceptable). 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, questions arise as to how to evaluate the consent documents that relate to the disposition of individual samples.

NBAC recommends that when research is conducted using existing identifiable samples, and where requirements to seek informed consent have not been waived, IRBs evaluate any existing consent documents for applicability. IRBs should use the following criteria to evaluate the applicability of such documents to the proposed research: [The Commission should develop these criteria. One criterion might be: Is

the proposed research consistent with the subject's likely understanding at the time the sample was obtained of how it might be used? The Commission might choose to note that IRBs should in some cases appropriately judge consent to unspecified future uses as sufficient consent for proposed research. In such cases, it may be appropriate to inform subjects of the research and in certain cases also give them the opportunity to "opt out."]

[The following text provides examples of possible approaches and is provided for the purpose of discussion.]

ELSI Working Group (1995): "Before requiring that a source be re-contacted to obtain consent, the investigator and the IRB should determine whether the person who provided the sample previously agreed to the use of the sample for genetic research. 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. By contrast, rarely does the language in typical operative and hospital admission consent forms provide an adequate basis for inferring consent to genetic research. If the IRB determines that the proposed research was agreed to by the source at the time the sample was obtained, then there is no need for further consent, although the IRB may choose to require that the investigator inform the sources, if still alive, about the new project and provide general news about the results."

National Heart, Lung, and Blood Institute (NHLBI, 1997) lists several issues for IRBs and funding agencies to consider "[i]n judging the adequacy of a previous informed consent when an application is received to do new genetic research": "(1) the nature of the disease proposed for study, (2) the likelihood that knowing results of the research will harm or benefit an individual, (3) the availability of effective treatment or prevention for the disorder, and (4) the burden of such treatment."

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 applicable, the individual can be offered the option of giving consent to the specific proposed protocol, and then offered the option of deciding how the sample may be used in the future.

NBAC recommends that when it is determined that existing identifiable materials were not collected with proper disclosure that the sample may be used in future research studies, and requirements to seek informed consent have not been waived, subjects should be offered the following options:

a) consenting to the proposed protocol;

b) stating that the sample cannot be used for any future research uses;

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

or

d) giving a blanket consent to identifiable uses of the sample in the future, with a written assurance that:

1) every reasonable effort will be made to ensure the source and their physician will be advised of research results that may affect the subject's well-being; and

2) appropriate measures will be taken to ensure confidentiality regarding the sample (appropriate measures might, for example, include the use of certificates of confidentiality).

If this proposal were implemented it would be crucial to inform sources who chose the option of rendering their samples unidentifiable that they would thereby be eliminating the possibility that future uses might reveal information from which they or their biological relatives might benefit.

The rationale for including the option of blanket consent in the case 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 give blanket consent to all lawful future uses or to have their samples rendered unidentifiable for future uses can be viewed as an effort to repair this deficiency. Even if blanket consent 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 a person now that the sample already taken from him may be used for purposes of which he had no inkling at the time of collection may not be adequate.

This policy for existing samples should be supplemented with a "special scrutiny" selective consent approach. In other words, if the source of an identifiable existing sample chose the option of not rendering the sample unidentifiable and giving blanket consent to future identifiable uses, he would enjoy the additional protection afforded by the requirement of specific consent for those uses of his sample that fall into a "special scrutiny" category. Such a category might include certain behavioral genetics protocols or research where the subject matter is particularly controversial. *[Please note: The Commission may wish to develop more fully the discussion of a "special scrutiny" category of research.]*

NBAC recommends that where research is proposed that falls into a "special scrutiny" category (i.e., protocols involving particularly controversial areas of research) and where the source of an existing identifiable sample has given blanket consent for future uses of his or her sample, the individual should be given the opportunity to "opt out" of the research.

Because it gives weight both to the source's interest in confidentiality and to their interest in being able to benefit from future research findings, this proposal better reflects a fair balancing of the relevant interests than a policy requiring that all future uses must be specifically consented to or conducted on unidentifiable samples.

Re-contacting Individuals

[Please note: The Commission has not discussed the details of the conditions under which re-contact should be required or conducted.]

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 (condition #4 of the waiver of consent);
- 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, different criteria should be used to determine whether re-contacting the individual is the appropriate course of action. Further, different concerns should be addressed when developing a plan to re-contact any individuals.

NBAC recommends that investigators and IRBs determine whether there is a need to re-contact subjects and, where this need exists, IRBs review the plan to re-contact the individual. In reviewing this plan the IRB should pay particular attention to the following issues: [The Commission needs further discussion to elucidate these issues.]

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. 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 with the possibility of a resulting requirement for obtaining express 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, and more important, 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 the clinical investigator, who might

wish to obtain additional samples, or who might wish to selectively go back and 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 different type of opposition to this practice is based on the belief that rendering samples unidentifiable without consent is problematic because researchers once had the opportunity to seek consent but did not exercise it.

The Commission believes that the need to render existing samples unidentifiable in order to expedite research protocols can be avoided in some 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 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 might be required.

NBAC recommends that investigators always be reminded of their duty to design studies using human biological materials in such a way as to minimize the risks to the sources of the biological materials, thereby improving the likelihood that the scientific value of the samples can be retained while simultaneously protecting the interests of the sample sources.

NBAC recommends that IRBs ensure that the reasons given by investigators for stripping identifiers from samples are appropriately justified as part of the design of a protocol. NBAC strongly encourages investigators to discuss, in advance, with IRBs their rationale for removing identifiers from samples.

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 an infinitesimally 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 concluded 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 standard review for quality and ethical acceptability.

COLLECTION OF HUMAN BIOLOGICAL MATERIALS IN THE FUTURE

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.

When samples are collected in a research or clinical setting, in addition to specific consent for the procedure or protocol for which the sample is being taken, 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.

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 relevant information. Persons who oppose revealing interim

findings argue that the harms that could result from revealing preliminary data whose interpretation changes when more precise or reliable data become available are serious, including anxiety or irrational (and possibly harmful) medical interventions. They argue that such harms are avoidable by controlling the flow of information to subjects and limiting communications to those that constitute reliable information. MacKay (1984), writing about the development of genetic tests, argues against revealing interim findings, contending that preliminary results do not yet constitute "information" since "until an initial finding is confirmed, there is no reliable information" to communicate to subjects, and that "even...confirmed findings may have some unforeseen limitations" [p. 3]. He argues that subjects should not be given information about their individual test results until the findings have been confirmed through the "development of a reliable, accurate, safe and valid presymptomatic test" [pp. 2-3; see also Fost and Farrell (1990)]. Others have argued that 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. He suggests that at least the following three factors be considered: "1) the magnitude of the threat posed to the subject; 2) the accuracy with which the data predict that the threat will be realized; and 3) the possibility that action can be taken to avoid or ameliorate the potential injury" [p. 5]. IRBs should ask investigators to define

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

CONSIDERATIONS OF RISKS AND POTENTIAL BENEFITS 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 strict focus that the regulations place on the individual research subject is arbitrary from an ethical standpoint, for the potential harms that the individual research subject may suffer are harms that other persons can also suffer as a consequence of the research.

NBAC recommends that investigators doing research on human biological samples (a) consider potential harms to persons who are not the (identifiable) sources of the samples in the specification of risks which a protocol poses, (b) minimize these risks in the design and implementation of a protocol where feasible, and (c) consider the implications of disseminating research results where such results may identify

individuals at risk of harm who are not the subjects, per se, of the research.

NBAC recommends that IRBs assess whether investigators have satisfied requirements (a)-(c) and whether, overall, the risks of harm to persons who are not research subjects are reasonable in relation to the anticipated benefits of the research.

[Please note: the language in the remainder of this section was suggested via e-mail after the Portland meeting so it needs further discussion. In addition, it is not clear what would trigger the need for an investigator to take this to an IRB. Although the Commission has determined that "others" should not be considered human subjects for the purpose of gaining consent, it has discussed whether their interests should be considered (although in what way has not yet been determined). Nevertheless, if the Commission concludes that "harms to others" should be considered, this may require changes in existing regulations governing institutional review board scrutiny of protocols]

Considerations of Risks and Potential Benefits to Groups

Research on (identifiable or unidentifiable) samples that implicate a racial or ethnic group may place group members at risk of being perceived as unusually prone to disease. For example, members of the group could consequently face stigmatization and discrimination in insurance and

employment. IRBs should give careful consideration to the definition of "group," especially in the case of persons with the same genetic conditions or diseases, so that not any research on any disease would qualify as research on a group.

OPRR guidance to IRBs and investigators on how best to address these matters 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 federally mandated Task Force on Participatory Research. NBAC supports this recommendation and encourages further efforts to develop strategies for protecting persons who are not currently defined as "human subjects."

Besides IRB examination, it seems appropriate to highlight how these sorts of 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 reinforce the worst sorts of 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) outweighs the harms that come from "labeling" a group as "high risk."

Considerations of Risks and Potential Benefits to Relatives of the Sample Source

A subset of the consideration of 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 of a genetic nature (where DNA, and therefore risks, may be shared by family members) or diseases that involve infectious agents or 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.[6] NBAC does not assume that because there might be risks to first-degree relatives of the sample source, those risks warrant considering those individuals to be human subjects, deserving the protection of informed consent. 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 considered, the Commission recognizes that there might be circumstances in which an investigator finds it useful, beneficial, appropriate, and feasible to discuss potential harms and benefits with such individuals.

[6] 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.

Considerations of Risks and Potential Benefits to Living Relatives of the Deceased

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.[7] 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.

[Please note: The Commission needs to discuss if there are ever any circumstances in which relatives could be considered identifiable research subjects and therefore, if the risk to them is more than minimal, their consent is required for the use of the dead person's samples. This is different than NBAC concluding that they are not human subjects when the sample source is still alive.]

[7] 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).

THE NEED FOR PUBLIC AND PROFESSIONAL EDUCATION

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 concerted public policy on use of human biological materials for research. As it stated in NBAC's 1997 report Cloning Human Beings,

> ***NBAC recommends 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.***

This recommendation encompasses the kinds of issues raised by storage and use of human biological materials and the implications of such research on important value systems. 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.

> ***NBAC recommends that OPRR begin an education program for the research community and IRBs to ensure that the regulations are clearly understood and followed,***

including more definitive 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."

NBAC recommends that when submitting research for publication, investigators must indicate to journal editors whether the samples used in the research were obtained from identifiable human subjects, whether (and to what extent) informed consent was obtained, and whether prior approval by an IRB was obtained. *[Note: The Commission may wish to include this recommendation with others relating to "research design".]*

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