

**Response of the  
Department of Health and Human Services  
to NBAC's Report  
Research Involving Human Biological Materials:  
Ethical Issues and Policy Guidance**

5/18/01

Harold Shapiro, Ph.D., Chair  
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Dear Dr. Shapiro:

I am pleased to provide you and the National Bioethics Advisory Commission (NBAC) with the response of the Department of Health and Human Services to your report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. The NBAC report is indeed a valuable contribution to the national discourse on the ethical issues related to the use of human biological materials in biomedical research. It will also help inform some of the relevant policy decisions that may need to be made by DHHS.

The Departmental response was prepared by a DHHS interagency working group consisting of representatives from the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the Indian Health Service, the Office for Human Research Protections, the Office of General Counsel and the Office of the Assistant Secretary for Planning and Evaluation. I believe that the document prepared by this working group provides a thoughtful and well reasoned response to the recommendations made by NBAC.

Sincerely,

William F. Raub, Ph.D.  
Acting Assistant Secretary for  
Planning and Evaluation

Enclosure



# EXECUTIVE SUMMARY

## Introduction and Overview

The National Bioethics Advisory Commission (NBAC) has identified research involving human biological materials as an increasingly important component of biomedical research and an area in which there is need to enhance the protection of human subjects involved in research. In August, 1999 NBAC issued a report titled *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*. The report offers 23 recommendations directed at researchers, institutions, Institutional Review Boards (IRBs), federal agencies and/or other components of the biomedical research and human subject protection enterprises. NBAC has requested that the Department of Health and Human Services (DHHS) review and provide a response to its report. To this end, the Office of Science Policy of the Office of the Assistant Secretary for Planning and Evaluation convened a multi-agency Working Group to analyze the appropriateness, feasibility and practical implications of implementing NBAC's recommendations and to develop a set of proposed DHHS activities to enhance the protection of human subjects in research involving human biological materials.

The Working Group commends NBAC for its careful analysis and far-reaching recommendations. NBAC's report will undoubtedly inform DHHS policy regarding human subject protection over the next several years and beyond. The Working Group concurs with a significant majority of NBAC's recommendations, either in principle or precisely as stated. In a few instances, detailed in this document, the Working Group foresaw some practical problems in implementation of specific recommendations. With a few appropriate exceptions, the Working Group developed proposed actions for each of NBAC's recommendations.

The Working Group recognizes that, until such time as federal regulations are revised through legislation or rulemaking, any enhancements to federal oversight of human subject protection must be carried out within existing regulations. The Working Group looks forward to NBAC's forthcoming report on *Ethical and Policy Issues in Research Involving Human Participants*, which is expected to make recommendations for broad changes in regulations. While the nature and extent of regulatory changes, if any, are not predictable, the Working Group believes that a number of important NBAC recommendations should be implemented as soon as possible. Therefore, for certain of NBAC's recommendations, the Working Group considered not only what enhancements could be made under current regulations but also what changes could be implemented by investigators and institutions on a voluntary basis.

Several of NBAC's recommendations address disclosure of research results to subjects. While NBAC has circumscribed the instances in which an investigator may disclose research findings to study subjects, the recently issued Health Insurance Portability and Accountability Act (HIPAA) privacy regulation established the rights of subjects to access information about themselves, including research results. Because some aspects of NBAC's recommendations are not compatible with the HIPAA privacy regulation, this issue requires further analysis.

The Working Group also recognizes that an increasing amount of human biological materials research involves genetic testing or genetic information<sup>1</sup>. Such research may or may not result in more than minimal risk to the human subjects who provide the materials but is often assumed to be of high risk by virtue of being a genetic study. The Working Group suggests that Institutional Review Boards (IRBs) review such research against specific criteria and not assume that genetic studies intrinsically pose more than minimal risk.

Brief summaries are provided below of the Working Group's analysis and proposed actions for each of NBAC's recommendations. The recommendations have also been summarized and are organized in clusters identical to the groups in NBAC's report.

### **Recommendations Regarding Interpretation of the Existing Federal Regulations**

*Summary of Recommendations and Discussion:* Recommendations 1 and 2 address the circumstances under which research conducted with human biological materials should be considered human subjects research and when such research is exempt from current federal regulations. In Recommendation 1, NBAC proposes that (a) research conducted with unidentified samples not be considered human subjects research, (b) research conducted with anonymized samples be considered human subjects research that may be exempt from regulations, and (c) research conducted with identified or identifiable samples be considered human subjects research that could be exempt from regulations only under specific conditions. While the Working Group agrees with substantial portions of Recommendation 1, analysis revealed significant impediments to practical applications of parts of this recommendation. In Recommendation 2, NBAC suggests, and the Working Group concurs, that the purpose for which human biological materials were originally collected, i.e., whether for research or for clinical purposes, should not determine whether research using such samples is eligible for expedited review by IRBs.

*Summary of Proposed Actions:* In response to Recommendation 1, the Working Group proposes that the Office for Human Research Protections<sup>2</sup> (OHRP), in consultation with FDA, (1) reinforce existing guidance that holds institutions, not investigators, responsible for determining whether or not research is subject to Regulations<sup>3</sup>, (2) ensure that institutions have policies and procedures for making such determinations and (3) broadly disseminate current

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<sup>1</sup> Widely varying definitions for “genetic testing” and “genetic information” have been proposed and/or adopted by professional associations and advisory committees, in legislation, and in regulations. The charge to the Working Group did not include a mandate to define these terms.

<sup>2</sup> References to OHRP in this report also refer, whenever applicable, to OHRP's predecessor organization, the Office for Protection from Research Risks (OPRR).

<sup>3</sup> The Working Group refers to the body of DHHS human subject protection regulations as “the Regulations”.

guidance that is applicable to determining whether research involving coded human biological materials meets the definition of human subjects research. In response to Recommendation 2, the Working Group proposes that DHHS implement NBAC's suggestion through publication of a federal register notice stating that research using human biological materials originally collected for research purposes may be eligible for expedited review if the newly proposed research poses no more than minimal risk to study participants.

### **Recommendation Regarding Special Concerns About the Use of Unlinked Samples**

*Summary of Recommendation and Discussion:* In Recommendation 3, NBAC focuses on the conditions that must be met by an investigator proposing to anonymize samples that are already in his or her control before his/her research can be recognized as exempt from the Regulations. NBAC proposes, and the Working Group agrees, that before research using such samples is deemed exempt from human subject protection regulations, institutions must ensure that the process used to anonymize samples is effective. NBAC also addresses the concern that research with anonymized samples may “unnecessarily reduce the value”<sup>4</sup> of the research. While the Working Group shares NBAC's concern on this issue, analysis identified practical obstacles to implementation of Recommendation 3(b).

*Summary of Proposed Action:* The Working Group proposes that DHHS explore the feasibility of collaborating with appropriate professional and scientific societies to develop educational materials on methods for anonymization of human biological materials.

### **Recommendations Regarding Requirements for Investigators Using Coded or Identified Samples**

*Summary of Recommendations and Discussion:* The Working Group concurs with both Recommendations 4 and 5, which address the need to protect the identity of individuals who are sources of human biological materials used in research. Recommendation 4 highlights the role and responsibilities of repositories, and Recommendation 5 describes information that IRBs should require from investigators before approving research with human biological materials that are or can be linked to human subjects.

*Summary of Proposed Actions:* In response to Recommendation 4, the Working Group proposes that OHRP, in consultation with FDA, review the adequacy of existing guidance and disseminate that which remains current to repositories that are subject to the Regulations, and undertake outreach to encourage repositories not subject to federal oversight to adopt this guidance. While Recommendation 5 does not require specific DHHS action, the Working Group proposes that OHRP, in consultation with FDA, work to increase awareness of relevant guidance and other educational materials that are useful in the preparation and review of research proposals.

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<sup>4</sup> NBAC Report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* at page 61, Recommendation 3 (b).

## **Recommendations Regarding Obtaining Informed Consent**

*Summary of Recommendations and Discussion:* Recommendations 6 through 9 address the process of obtaining informed consent for the research use of human biological materials. The Working Group concurs with Recommendation 6, which addresses the need for separating consent for research from consent for clinical procedures. The Working Group agrees with Recommendation 7 regarding an individual's right to decline to participate in research and with Recommendation 8 regarding interpretation of existing consents with respect to research that was not foreseen at the time the original consent was obtained. For Recommendations 7 and 8 the Working Group identified issues that should be considered with a view toward assuring that implementation of NBAC's recommendations enhances human subject protection and biomedical research. Finally, the Working Group concurs with Recommendation 9, which addresses the consent options that could be offered to potential research subjects with respect to use of their human biological materials in research.

*Summary of Proposed actions:* In response to Recommendation 6, the Working Group proposes that OHRP, in conjunction with NIH, FDA, CDC and other appropriate DHHS agencies, sponsor a workshop on informed consent to assist in determining what additional studies are needed and what additional guidance might be developed by OHRP in conjunction with other appropriate agencies. In response to Recommendation 7, the Working Group proposes that OHRP, in consultation with FDA, reinforce the need for appropriate training of individuals who are responsible for obtaining informed consent, as well as the need to ensure that the right to decline to participate in research is clearly stated in consent forms. In response to Recommendation 8, the Working Group proposes that OHRP, in consultation with FDA, take the lead in developing guidance on evaluating the adequacy of extant consent documents. In response to Recommendation 9, the Working Group proposes that DHHS continue to fund studies in this area and disseminate the results of such studies.

## **Recommendations Regarding the Criteria for Waiver of Consent**

*Summary of Recommendations and Discussion:* Recommendations 10 through 13 address four criteria in federal regulations that govern waiver of consent. Each of these recommendations is tied to one of four criteria, all of which must be satisfied before a waiver of consent may be granted. These criteria require the researcher to demonstrate that (1) the research poses minimal risk to subjects, (2) there is no adverse effect on subjects' rights and welfare, (3) it would be impracticable to obtain consent, and (4) subjects will be provided, whenever appropriate, with additional pertinent information after completion of the study. The Working Group concurs with NBAC's four recommendations for application of these criteria to research involving human biological materials. However, the Working Group notes that, for research regulated by the FDA, rules governing waiver of consent are more restrictive. The Working Group also considered some practical issues that must be addressed with respect to whether and how findings from a study conducted under a waiver of consent may be shared with a study subject. Finally, the Working Group identifies some issues that would not be resolved by implementing Recommendation 12 at a specific point in time.

*Summary of Proposed Action:* The Working Group proposes that OHRP, in consultation with FDA, prepare and disseminate guidance to support implementation of Recommendations 10-13.

### **Recommendations Regarding Reporting Research Results to Subjects**

*Summary of Recommendations and Discussion:* Recommendations 14 through 16 address the disclosure of research results to subjects. The Working Group considered these recommendations with respect to both disclosure initiated by the researcher and disclosure at the request of the subject. Recommendation 14 outlines conditions that should be met before research results may be reported to subjects. The Working Group notes that Recommendation 14 appears to be in conflict with some provisions of the HIPAA privacy regulation which was issued after NBAC completed its report. If such conflict could be resolved, the Working Group agrees that only valid information should be disclosed but is troubled by the remaining two criteria that are to be met before results can be disclosed to subjects. The Working Group concurs with Recommendations 15 and 16, which require researchers to identify the circumstances under which research results warrant disclosure, to develop a plan for managing such disclosure, and to provide appropriate medical advice or referral when disclosure is made.

*Summary of Proposed Actions:* The Working Group proposes further analysis of Recommendation 14. The Working Group proposes that OHRP, in consultation with FDA, develop and disseminate guidance for implementation of Recommendations 15 and 16.

### **Recommendations Regarding the Considerations of Potential Harms to Others**

*Summary of Recommendations and Discussion:* Recommendations 17 and 18 address the need to minimize the risk of harm to groups associated with the individuals who are the sources of the human biological materials to be used in research. The Working Group agrees with the suggestion in Recommendation 17 that investigators should plan research to minimize such risks and should, when appropriate, consult with representatives of relevant groups in planning research that could pose such risks. The Working Group is persuaded that further work is needed to identify appropriate methods for consultation with representatives of groups. While it is appropriate for IRBs to consider risk of group harm even for studies conducted with anonymized samples, the current regulations do not provide a mechanism for DHHS to require IRB review of such studies. The Working Group agrees with Recommendation 18, which states that risk of group harm should be disclosed during the process of obtaining informed consent for research.

*Summary of Proposed Actions:* While awaiting NBAC's recommendations regarding group harm in its forthcoming report on federal oversight of human subject protection, the Working Group proposes that DHHS encourage studies of strategies, including those suggested in Recommendation 17, to minimize group harm. The Working Group proposes that OHRP, in consultation with FDA, develop guidance for implementation of Recommendation 18.

## **Recommendations Regarding the Publication and Dissemination of Research Results**

*Summary of Recommendation and Discussion:* Recommendation 19 addresses the risk that dissemination of research results could cause harm to subjects or groups with which subjects are associated. The Working Group agrees that investigators should consider such risks and make efforts to reduce them. The Working Group also agrees with Recommendation 20, which urges journals to adopt a policy that would require published results of research studies to include a statement about whether research was conducted in compliance with federal human subject protection regulations, regardless of whether or not the research was subject to federal regulatory oversight.

*Summary of Proposed Actions:* No DHHS action is required.

## **Recommendations Regarding Professional Education and Responsibilities**

*Summary of Recommendations and Discussion:* The Working Group concurs with NBAC's Recommendations 21 and 22 regarding professional education and responsibilities. Recommendation 21 focuses on the need to continue and expand efforts to train investigators and to identify exemplary practices for protection of human subjects in research involving human biological materials. Recommendation 22 addresses the need for additional resources to ensure protection of human subjects. The Working Group agrees with this recommendation and also underscores the need to ensure appropriate utilization of existing resources.

*Summary of Proposed Actions:* In response to Recommendation 21, the Working Group proposes that DHHS continue ongoing activities and coordinate such efforts throughout the Department. In response to Recommendation 22, the Working Group proposes that DHHS continue to work with awardee institutions to highlight the importance of adequate support for human subject protection activities.

## **Recommendation Regarding the Use of Medical Records in Research on Human Biological Materials**

*Summary of Recommendation and Discussion:* Recommendation 23 points out that there are similarities between research using human biological materials and research using medical records and calls upon those drafting medical records privacy laws to harmonize rules governing the two types of research. The Working Group concurs with this recommendation, but calls attention to the fact that there are also important differences between these two areas of research.

*Summary of Proposed Action:* No DHHS action is required.

**Analysis and Proposed Actions Regarding  
The National Bioethics Advisory Commission (NBAC) Report  
*Research Involving Human Biological Materials:  
Ethical Issues and Policy Guidance***

**Introduction**

Protection of individuals who participate in research as human subjects is a vital public policy. Volunteers willing to assume the risks associated with participating in research have been the cornerstone of many of the medical advances that we enjoy today. Without the involvement of human subjects, much biomedical research, including a significant share of basic research, would not be possible. While ensuring the scientific community's ability to pursue its goals of developing new knowledge and more effective means of preventing, diagnosing and treating illnesses and disorders, we also must take measures to protect those who participate in research. A strong ethical foundation should go hand in hand with a robust scientific enterprise. Vigorous human subject protections also help to maintain public confidence in this enterprise; this confidence makes possible the continuous strong support the American public has given to our pursuit of biomedical research.

With the rapid, cutting-edge technological advances that have been made in recent years, ethical issues have emerged in a variety of unexpected areas – requiring scientists, ethicists and the public to examine the sometimes contradictory interplay between the pursuit of scientific goals and respect for society's values. Research involving human biological materials – a promising and rapidly growing field – is one arena in which a number of important ethical issues have emerged.

The National Bioethics Advisory Commission's report, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, is a thoughtful and insightful document that will help inform policymaking in the Department of Health and Human Services (DHHS). Much biomedical research involves some degree of risk to study participants. It is not clear to what extent the public is aware that there is sometimes a correlation between what can be learned from research and the level of risk to which participants are exposed. This relationship is especially true in research involving human biological materials. Research based on use of human biological materials can be carried out with virtually no risk to the individuals from whom samples were originally collected when the samples have been divorced from any personal identifiers. In such instances, however, the investigator is then unable to obtain additional information about the sample sources that would help to determine if a research finding correlates with development of disease or with beneficial or adverse response to a new therapy. NBAC's report speaks to the importance of balancing the protection of human subjects with the pursuit of new biomedical knowledge that may be relevant to safeguarding and strengthening the public's health and welfare.

NBAC's recommendations, covering both publicly and privately funded research, are intended for not only DHHS and its component agencies but also broad segments of the scientific community, including researchers, institutions, repositories, institutional review boards and the

public. In order to analyze the appropriateness, feasibility and practical implications of those recommendations directed at DHHS, the Office of Science Policy of the Office of the Assistant Secretary for Planning and Evaluation convened a multi-agency Working Group to review and provide a response to NBAC's report. The Working Group included representatives from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), and the National Institutes of Health (NIH). Also included in the Working Group were representatives of the Office of General Counsel (OGC) and the Office for Human Research Protections (OHRP).

The Working Group agreed with and endorsed almost all of NBAC's analyses and recommendations. In a few instances, the Working Group foresaw some practical problems that would result from implementation of the recommendations; these difficulties are described below. Whenever appropriate, the Working Group proposed specific actions that could be taken by DHHS to strengthen the oversight of research involving human biological materials.

### **General Comments**

In preparing this response to NBAC's report, the Working Group recognizes that, until such time as federal regulations are revised through legislation or rulemaking, any enhancements to federal oversight of human subjects protection must be carried out within the construct of existing regulations. Furthermore, the Working Group is mindful that NBAC has spent considerable time conducting a major examination of the current framework, regulations and policies for the protection of human subjects in research and has published for public comment a draft report entitled *Ethical and Policy Issues in Research Involving Human Participants*. When completed, this report is expected to make recommendations for broad regulatory changes whose scope probably will include research involving human biological materials. However, since the nature and extent of the eventual regulatory changes, if any, are not predictable now, the Working Group believes that a number of important NBAC recommendations should be implemented as soon as feasible. Therefore, for certain of NBAC's recommendations, the Working Group considered not only what enhancements could be made under current regulations but also what changes could be implemented by investigators and institutions on a voluntary basis. The actions the Working Group proposed in response to NBAC's report can be implemented without the complex and time consuming efforts involved in promulgating new regulations.

### **Discussion of Terms Used in Report**

Certain terms or phrases used throughout the Working Group's response require some explanation.

#### **Office for Human Research Protections (OHRP)**

Between the time NBAC issued its report and the development of this DHHS response, the Office for Human Research Protections (OHRP) was created in the Office of Public Health and Science, as a staff office within the Office of the Secretary of Health and Human

Services. OHRP has assumed the human subjects protection role previously vested in the Office for Protection from Research Risks (OPRR) at NIH. Therefore, references to OHRP in this report also refer, whenever applicable, to the former OPRR.

#### Definitions of types of human biological samples

NBAC classifies samples in accordance with their level of identifiability. The Working Group agrees with NBAC categories but has some reservations about the introduction of the new label “unlinked samples”. NBAC’s definition of “unlinked samples” is the same as the definition of the more commonly used term “anonymized samples.” The Working Group sees no advantage in introducing new nomenclature and suggests maintaining use of the already recognized term “anonymized samples.” Continuing to use the term “anonymized” has the advantage of permitting easy reference to current and emerging literature and educational materials on this subject. Moreover, “anonymized” is more commonly understood, self explanatory and more precise.

#### References to federal regulations governing human subjects protection

“Common Rule” refers to Subpart A of 45 CFR Part 46 and is broadly understood as a shorthand for federal regulations that govern the protection of human subjects in research. However, while the Common Rule applies to research conducted, supported or regulated by any federal Department or Agency that has issued regulations equivalent to Subpart A, other DHHS regulations also apply to human subjects protection. 45 CFR Part 46 Subparts B, C and D, respectively, provide additional safeguards for subjects who are pregnant women, prisoners or children. There are, in addition, significant differences between 45 CFR Part 46 and 21 CFR Parts 50 and 56 (regulations applying to FDA-regulated research only). For example, unlike the Common Rule, FDA regulations do not describe a human subject in terms of a living individual about whom data is collected through intervention or interaction or identifiable private information. Moreover, the criteria for waiver of informed consent differ substantially. FDA regulations require Institutional Review Board (IRB) review and approval of all FDA-regulated research involving human subjects. Thus, some of NBAC’s recommendations may not apply to certain research regulated by FDA.

In carrying out analysis and developing a response to NBAC’s report, the Working Group considered all applicable human subjects protection regulations. To simplify references in this report to this set of regulations, the Working Group adopted the convention of using the term “the Regulations” to refer to either or both 45 CFR Part 46 and 21 CFR Parts 50 and 56 depending upon the context of the discussion.

Research utilizing human biological materials may:

- < be covered by the Regulations;
- < be exempt from the Regulations;
- < not involve human subjects as defined by the Regulations and therefore be not subject to the Regulations;
- < or, for other reasons, be outside the jurisdiction of the Regulations.

The Working Group found that efforts to maintain these distinctions at all times were unwieldy and cumbersome. Therefore, throughout this document, the Working Group uses phrases such as “not covered by the Regulations,” “the Regulations are not applicable” or “not subject to the Regulations” to refer to any instance(s) in which the Regulations do not apply.

Finally, the Working Group notes that the phrase “exempt from IRB review”<sup>1</sup> appears in several places in the NBAC report. Although historically it is not clear when this phrase was first introduced in discussions of IRB roles and responsibilities (it also appears in OPRR/OHRP guidance), the Working Group points out that, while the Regulations identify what is or is not exempt from the Regulations, they do not provide a mechanism to *exempt a proposal from IRB review* (emphasis added). Because this phrase could be misleading, the Working Group urges that, in future communications and documents, the phrase be replaced with more precise language.

### **Specific Issues of Note**

#### **Privacy and Individual Right of Access to Personal Health Records**

Subsequent to completion of NBAC’s report, DHHS issued the Health Insurance Portability and Accountability Act (HIPAA) regulation on privacy of health records entitled *Standards for Privacy of Individually Identifiable Health Information*. After considering additional public comment on the final rule, President Bush reaffirmed that the privacy rule would be effective on April 14, 2001, and that guidance or recommended modification of the rule would be forthcoming in the near future. Currently, this regulation provides an individual the right of access to information about himself or herself, including personal research results, with limited exceptions. While the Privacy Act of 1974 has similar provisions that affect records held by federal agencies, the new HIPAA regulation has markedly changed the landscape with respect to disclosure of information and thereby is in conflict with some of NBAC’s recommendations. This issue is treated more extensively in the Working Group’s response to Recommendation 14.

#### **Genetics Research**

As time passes, an increasing share of human biological materials research is likely to be in the area of human genetics. Anecdotal information suggests that some IRBs appear to be particularly cautious when reviewing genetic studies. Some IRBs assume that any research involving genetics is likely to be more than minimal risk, even if the study uses proven strategies to minimize risk. That is not necessarily so. The Working Group suggests, therefore, that IRBs need specific guidance to deal with genetic studies. That guidance should emphasize to IRBs that research involving genetic testing or genetic information<sup>2</sup> should be evaluated against specific criteria (either existing or, if existing criteria are inadequate, new criteria), and not judged to be more than minimal risk simply by virtue of involving genetics.

## **Future Considerations**

Given the rate at which scientific advances are being made, there should be recognition that recommendations made, guidance issued, or regulations promulgated today may be inadequate to address research-related ethical concerns in the future. Therefore, the Working Group recommends re-examination from time to time as necessary of the guidance and regulations governing human subjects protection.

## **Comments on Specific Recommendations**

This section presents the Working Group's response to each of NBAC's 23 recommendations. While most recommendations are addressed separately, some are grouped because they constitute logical clusters with certain commonalities. Each response begins with the text of the recommendation, then presents the Working Groups analysis and concludes with the Working Group's proposed action.

### **Recommendations Regarding Interpretation of the Existing Federal Regulations**

**Recommendation 1.** *Federal regulations governing human subjects research (45 CFR 46) that apply to research involving human biological materials should be interpreted by the Office for Protection from Research Risks (OPRR), other federal agencies that are signatories to the Common Rule, IRBs, investigators, and others in the following specific ways:*

- a) *Research conducted with unidentified samples is not human subjects research and is not regulated by the Common Rule.*
- b) *Research conducted with unlinked samples is research on human subjects and is regulated by the Common Rule, but is eligible for exemption from IRB review pursuant to 45 CFR 46.101(b)(4).*
- c) *Research conducted with coded or identified samples is research on human subjects and regulated by the Common Rule. It is not eligible for exemption unless the specimens or samples are publicly available as defined by 45 CFR 46.101(b)(4). Few collections of human biological materials are publicly available, although many are available to qualified researchers at reasonable cost. Therefore, OPRR should make clear in its guidance that in most cases this exemption does not apply to research using human biological materials.*

## **Discussion**

NBAC's first recommendation offers guidance to "improve the interpretation and implementation of [the Regulations]"<sup>3</sup> with respect to human subjects research. NBAC proposes specific criteria, based upon the identifiability of samples, to determine whether a given research project involving human biological materials should be considered human subjects research. To place the discussion of this recommendation in context, the Working

Group refers to the definition of “human subject” in 45 CFR 46.102(f): *“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.”*

#### Recommendation 1(a)

The Working Group agrees with Recommendation 1(a), which is consonant with current interpretation of federal human subjects protection regulations.

#### Recommendation 1(b)

Although the Working Group agrees that there are instances in which study of anonymized human tissue is human subjects research, the Working Group is concerned that NBAC’s proposal in Recommendation 1(b) goes beyond the regulatory definition of human subjects research and raises questions about whether this broader interpretation is necessary or enforceable under current regulations.

NBAC defines “unlinked” or anonymized samples as those that “lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.” The Working Group agrees with this definition and notes that an appropriately and effectively anonymized sample is functionally indistinguishable from an unidentified sample. Therefore, the Working Group believes that use of appropriately and effectively anonymized samples presents no more and no less potential for harm to an individual than use of anonymous samples. Whether the sample was made anonymous at the time of collection, at some point following the collection, or just prior to usage in research, once the sample has been anonymized, it can no longer be linked to an individual. Consequently, the researcher using such samples cannot be said to be performing human subjects research. The Working Group remains persuaded that, in all but one important case (see response to Recommendation 3), research conducted with effectively unlinked or anonymized samples that cannot be identified by the researcher is not human subjects research and is therefore not covered by the Regulations.

The Working Group notes that whether or not a proposal involves human subjects research is not always obvious. Current regulations, supported by OHRP guidance, hold institutions – not the researcher – responsible for making such a determination.<sup>4</sup> Certification of whether a research project involves human subjects is only one example of the ways in which the system of human subjects protection relies upon institutional policies and practices, established under the Regulations and OHRP’s assurance process, to determine whether research is subject to the Regulations.

#### Recommendation 1(c)

While the Working Group agrees that all research on identified samples and most research on coded samples is research on human subjects, the Working Group notes that some research on

coded samples may fall outside the definition of human subjects research. In addition, the Working Group has serious concerns about NBAC's interpretation of the term "publicly available".

Coded samples can only be linked to individuals when the key needed to decipher the code is accessible. When the key exists but is inaccessible to the researchers and collaborators, those coded samples are effectively unlinked or anonymized for purposes of that research project. Since some important research is conducted using this model, OHRP has developed and published guidance for determining whether a researcher using coded samples is engaged in human subjects research.<sup>5</sup> OHRP has determined that if a repository operating under the Regulations has a written agreement with a researcher that prohibits the researcher and collaborators from gaining access to the key, then the researcher has no means of identifying the source of the sample and therefore is not engaged in research on human subjects. OHRP has also, on a case-by-case basis, extended the application of this guidance to other situations where a similar written agreement exists. The Working Group endorses this guidance, which recognizes circumstances in which research using coded samples is not human subjects research.

The above example demonstrates the difficulty of using categories of samples (unidentified, unlinked, coded, identified) exclusively to determine whether or not research involves human subjects. The Working Group recognizes that, in the day-to-day research environment, involvement of human subjects and degree of research risk do not always have a one-to-one correspondence with the types of human biological samples used.

The recently issued HIPAA privacy rule also addresses the issue of research conducted with coded information. HIPAA refers to information as "de-identified" if specific data elements have been coded and permits use of "de-identified" information for research without IRB review or patient authorization. Therefore, some research using coded samples may be covered by the Common Rule but exempt from the HIPAA privacy rule. The need to analyze the implications of the interaction between the HIPAA privacy rule and NBAC's recommendations is addressed in the Working Group's response to Recommendation 14.

The Working Group agrees with NBAC's statement that if coded or identified samples are publicly available, then research using these samples is exempt from the Regulations. However, the Working Group does not concur with NBAC's conclusion that "few collections of human biological materials are publicly available, though many are available to qualified researchers at reasonable cost."<sup>6</sup> The Working Group believes that NBAC's definition and examples of human biological materials that are "publicly available" are overly restrictive and would, if implemented, impede certain research that is otherwise exempt under 45 CFR 46.101(b)(4).

Although OHRP has no formal guidance on the definition of "publicly available", on a case-by-case basis OHRP has provided informal advice that interprets "publicly available" as commercially available or available in a reasonably unrestricted fashion. At times, OHRP has also interpreted "publicly available" as *widely available to responsible parties* (emphasis

added), especially if there is a statute or other legal requirement mandating such availability. OHRP's interpretation therefore recognizes that a research resource, such as a human biological materials repository, may meet the definition of "publicly available" even if access to the samples requires a reasonable commercial fee or handling charge and/or demonstration of the ability to manage the materials responsibly.

The Working Group calls attention to the American Type Culture Collection (ATCC), a source of publicly available samples, to illustrate that requiring the payment of commercial fees and demonstration of responsibility are compatible with the principle of public availability. The ATCC holds approximately 1500 cell lines that are derived from human cells. Catalogs of repositories such as the ATCC are freely available to the public. Access to its web sites, on which catalogs are posted, is also not restricted. Therefore, access to information about these cell lines is not constrained in any significant way. To obtain materials from ATCC, investigators pay a fee and sign an agreement stating that they will abide by ATCC rules regarding use of the materials, that they are qualified to work with the materials, and that they agree in writing to assume all risk and responsibility in connection with the receipt, handling, storage and use of the materials. Most of ATCC's human-derived cell lines have been distributed to thousands of laboratories over the last few decades.

For other types of human biological materials and repositories, arguments that samples are not publicly available are valid. Samples should not be considered publicly available if information about the existence of samples is available to only a select group. In addition, if only a small and select group can meet conditions required for release of materials, samples are not deemed to be publicly available. There is often a correlation between the type of sample (for example, a renewable cell line or a finite amount of the originally collected tissue) and the conditions that a repository imposes before release of samples. However, the correlation is not sufficiently strong to permit an unequivocal determination *a priori* about whether or not a given sample is publicly available.

The Working Group concludes that interpretation of the term "publicly available" must be sufficiently broad to permit application to a wide variety of repositories and to the human biological materials in their custody. The Working Group expects there will be instances in which it will not be absolutely clear whether samples are publicly available and therefore recommends that OHRP continue to provide advice on a case-by-case basis.

#### Proposed Action

The Working Group proposes that, with respect to existing guidance applicable to use of human biological materials in research, OHRP be charged with the following:

- < Conduct outreach and educational efforts to underscore existing OHRP guidance, which recognizes that research with "unlinked" or anonymized samples is not subject to the Regulations. This education should highlight the fact that it is the responsibility of the institution and not the prerogative of the individual researcher to determine whether or not a proposed research project is covered by the Regulations.

- < Require that all relevant institutions have policies and procedures for reviewing the validity of a researcher's assertion that a proposed research project involving human biological materials is not regulated by or is exempt from the Regulations. Such assertions should be reviewed by an IRB, or by a designated institutional official with appropriate training in human subjects protections, in accordance with current OHRP guidance.
- < With respect to determining whether or not research involving coded human biological materials meets the definition of human subjects research, broadly disseminate current guidance on reviewing written agreements between researchers and repositories to ascertain whether or not the key to the code will be made inaccessible to the research team.

Recommendation 2. *OPRR should revise its guidance to make clear that all minimal risk research involving human biological materials—regardless of how they were collected—should be eligible for expedited IRB review.*

### Discussion

The Working Group concurs with Recommendation 2 and agrees with NBAC that, for the purposes of determining eligibility for expedited IRB review, it is not necessary to draw a distinction between samples originally collected for clinical purposes and those obtained for research purposes. The Working Group also agrees with NBAC's observation that current guidance regarding the types of research that IRBs may review through expedited procedures (63 FR 60364-60367 [HHS] and 60353-60356 [FDA], November 9, 1998) appears to exclude research utilizing existing specimens previously collected for research purposes. It is the understanding of the Working Group that this apparent exclusion is not intentional but rather resulted from a copy editing oversight and that OHRP and FDA intend to publish a Federal Register Notice to correct this error.

### Proposed Action

The Working Group proposes that OHRP and FDA (a) publish a Federal Register Notice as soon as possible to explicitly state that research involving human biological materials originally collected for research purposes is eligible for expedited IRB review if the newly proposed research poses no more than minimal risk to the study participants and then (b) revise its guidance accordingly.

### **Recommendation Regarding Special Concerns About the Use of Unlinked Samples**

Recommendation 3. *When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, an IRB (or other designated officials at the investigator's institution) may exempt the research from IRB review if it determines that*

- a) the process used to unlink the samples will be effective, and*

*b) the unlinking of the samples will not unnecessarily reduce the value of the research.*

## Discussion

The Working Group concurs with the principle in Recommendation 3(a) that caution must be exercised when an investigator proposes to create anonymized samples from coded or identified materials already under his or her control. Unlinking samples reduces risk to the individual who is the source of the sample only if the process of anonymization is effective. The Working Group agrees with NBAC that policies and procedures are needed to ensure that the process of anonymizing samples is effective. The agent to certify that the anonymization process is effective should be the IRB or a designated institutional official.

With respect to Recommendation 3(b), the Working Group agrees with NBAC that unlinking of samples may reduce the potential value of the research. Therefore, IRBs should not discourage research involving use of coded samples when the proposal design includes appropriate protection for subjects and should grant waivers of consent when appropriate. On the other hand, since research with anonymized samples eliminates virtually any meaningful risk to the individuals who provided the samples, the Working Group does not share NBAC's concern that the effect of anonymization is to "circumvent"<sup>7</sup> protections for human subjects. In fact, anonymization provides the highest possible level of protection for human subjects because there are no means to identify the subjects.

There are, however, instances in which anonymization can increase risk to subjects. While research using anonymized samples involves minimal risk to the sample sources, it could, in certain research increase risk of harm to other research subjects. For example, inability to identify the sources of cells or tissues used to develop therapeutic products is a risk to the safety of the recipients of such products in clinical trials.<sup>8</sup> These risks may be sufficient to preclude use of materials developed under 45 CFR Part 46 in subsequent clinical investigations subject to 21 CFR Parts 50 and 56, thereby reducing the value of research intended to develop therapeutic materials from human sources. Regardless of the type of research being proposed, careful attention must always be given to assessing the balance of risks and benefits for all participants.

The Working Group has concerns about practical problems that may arise in implementing Recommendation 3(b). This recommendation requires an IRB or institutional official to consider whether anonymization of samples will "unnecessarily reduce the value of the research."<sup>9</sup> To consider whether the value of a given project is reduced requires the IRB or institutional official to compare the expected value of the proposal in question with the expected value of a nearly identical but hypothetical study conducted with identified or coded samples.<sup>10</sup> This requirement is impossible to meet at worst and at best could go well beyond the expertise of institutional officials responsible for determining whether proposals meet specific criteria provided in federal regulations. In addition, the requirement would expand the mandate or charge of IRBs, for IRBs' principal mission and focus must be the protection of human subjects in the research that is proposed.

### Proposed Action

The Working Group proposes that DHHS explore the feasibility of collaborating with appropriate professional and scientific societies to develop educational materials on methods for the effective anonymization of human biological materials to be used in research. If such an undertaking is determined to be feasible, such materials should be prepared and broadly disseminated to institutions and researchers. Furthermore, institutions receiving federal funds for biomedical research should provide instructions to investigators, where needed, on effective anonymization of human biological materials to be used in research.

### **Recommendations Regarding Requirements for Investigators Using Coded or Identified Samples**

*Recommendation 4. Before releasing coded and/or identified samples from its collection, a repository should require that the investigator requesting the samples either provide documentation from the investigator's IRB that the research will be conducted in compliance with applicable federal regulations or explain in writing why the research is not subject to those regulations.*

### Discussion

The Working Group concurs with Recommendation 4, which highlights the responsibility of repositories in protecting human subjects.

For those repositories operating under the Regulations, NBAC's Recommendation 4 should work in concert with existing OHRP guidance, which states that repositories should operate under IRB oversight.<sup>11</sup> It also provides for situations in which an investigator requesting coded samples signs an agreement with the repository indicating that he/she will not be provided with means to identify the samples. In such cases, the researcher is, in effect, working with anonymized samples and will have documentation to that effect.

It should be noted that there are situations in which the Federal Government has no jurisdiction over either the repository or the investigator. In such cases, where the parties are not governed by federal human subject protection regulations, opportunities for oversight may at best be limited. The Working Group urges that parties not subject to Federal oversight comply voluntarily with OHRP guidance.

### Proposed Action

The Working Group proposes that OHRP, in consultation with FDA, review for applicability and disseminate as appropriate its existing guidance on the type of information that repositories operating under the Regulations require in order to evaluate whether a proposed use of samples is in compliance with applicable federal regulations. These repositories should require all researchers to provide such information and documentation, use such information to determine

whether and how to release samples, and retain records to document their procedures and decisions.

Recommendation 5. *When reviewing and approving a protocol for research on human biological materials, IRBs should require the investigator to set forth*

- a) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects,*
- b) a full description of the process by which samples will be obtained,*
- c) any plans to obtain access to the medical records of the subjects, and*
- d) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.*

### Discussion

The Working Group concurs with Recommendation 5. Although the wording of this recommendation does not state so specifically, the recommendation addresses only research protocols involving the use of identified or coded samples since it appears, along with Recommendation 4, in a section that specifically addresses identified or coded human biological materials.

NBAC's Recommendation 5 clearly articulates those issues that must be considered by an IRB when evaluating a proposal for research involving identified or coded human biological materials. These requirements are consistent with 45 CFR 46.111(a) and 21 CFR 56.111(a), which require the IRB to determine that research procedures are consistent with sound research design and do not unnecessarily expose subjects to risk. Guidance relevant to Recommendation 5 is contained in the Institutional Review Board Guidebook: Chapter 3a (Risk Benefit Analysis),<sup>12</sup> Chapter 3d (Privacy and Confidentiality),<sup>13</sup> Chapter 4 (Considerations of Research Design)<sup>14</sup> and Chapter 5h (Human Genetic Research).<sup>15</sup> The responsibility of IRBs to evaluate the investigator's plan for maintenance of confidentiality is further elaborated in the memorandum "IRB Knowledge of Local Research Context",<sup>16</sup> which includes "method for protection of privacy of subjects" and "method for maintenance of confidentiality of data" as elements of the proposal that must be submitted to the IRB for review. Another provision of the memorandum requires IRBs to "determine and specifically document that provisions to protect the privacy of subjects and maintain the confidentiality of data are adequate."

The Working Group calls attention to a strategy that can be used to protect research subjects from certain types of disclosures of sensitive information. Where appropriate and available, an investigator may obtain a Certificate of Confidentiality<sup>17</sup> from DHHS. This permits the investigator to resist compulsory legal demands, such as subpoenas and court orders, for information identifying research subjects. Investigators and IRBs should be more aware of the potential value of these Certificates.

## Proposed Action

This Recommendation is directed at IRBs and is well covered by current OHRP guidance. However, the Working Group proposes that OHRP urge organizations such as Public Responsibility in Medicine and Research (PRIM&R) and the Applied Research Ethics National Association (ARENA) to increase awareness of pertinent guidance and educational materials that can assist IRBs in the review, and investigators in the preparation, of research protocols involving identified or coded samples.

## **Recommendations Regarding Obtaining Informed Consent**

Recommendation 6. *When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent to clinical procedures.*

## Discussion

The Working Group concurs with Recommendation 6. NBAC's recommendation is in keeping with 45 CFR 46.116 and 21 CFR 50.20, which require that consent be sought only "under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." NBAC points out, and the Working Group agrees, that individuals being asked to give informed consent to clinical procedures are often dealing with stressful health issues and complex paperwork. This may temporarily compromise the ability of a prospective research subject to thoroughly consider the relevant issues and effectively participate in the process of informed consent.

The Working Group notes, however, that it is not clear how such separation can best be achieved. Consent "obtained separately" could refer to the times at which consent is obtained, to the person who obtains consent, to separate consent documents, or to combinations of these options. Each of these alternatives has different implications for implementation. The Working Group observes that NBAC refrained from prescribing a specific answer to the question of how best to separate consent for clinical procedures from consent for research use of human biological materials. NBAC refers instead to the thoughtful input provided by other groups, including the National Action Plan for Breast Cancer, "on ways in which to improve the overall consent process, including its design and timing"<sup>18</sup> and concludes that additional studies are needed. The Working Group agrees and notes that DHHS is already supporting significant endeavors in this area.<sup>19</sup> One study in particular that deserves special mention is the field testing of the consent approach suggested by the National Action Plan for Breast Cancer.<sup>20</sup> The Working Group endorses NBAC's conclusion that "the scientific community should develop a consensus regarding a standard method for human biological materials collection in both therapeutic and research contexts – one that would minimize the need for complex efforts to recontact the source."<sup>21</sup>

### Proposed action

The Working Group proposes that OHRP, in conjunction with NIH, FDA, CDC and other appropriate DHHS agencies, sponsor a workshop on informed consent. The workshop, to be convened following NBAC's forthcoming report *Ethical and Policy Issues in Research Involving Human Participants*, should bring together investigators of DHHS-funded studies on informed consent, IRB members, and representatives of relevant professional societies and lay advocacy groups to review current knowledge, share findings from recent studies, suggest future avenues of research, and discuss various approaches for obtaining informed consent and their relative effectiveness and practicality. Results from this workshop will assist OHRP in determining what additional studies may need to be funded and what guidance might appropriately be developed in consultation with relevant DHHS agencies.

Recommendation 7. *The person who obtains informed consent in clinical settings should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.*

### Discussion

The Working Group concurs with the principles underlying Recommendation 7. NBAC's recommendation emphasizes the importance of the protection required by 45 CFR 46.116 and 21 CFR 50.20. In particular, 46.116(a)(8) and 21 CFR 50.25(a)(8) state that the potential research subject must be informed that participation is voluntary and that "refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled," and that the same rights apply to an individual who initially participates in and later withdraws from a study. No one should be denied routine clinical care that he or she would otherwise be receiving as a result of declining to participate in a research study. Although OHRP guidance titled "Informed Consent Checklist"<sup>22</sup> and FDA's information sheet titled "A Guide to Informed Consent"<sup>23</sup> already require that this issue be addressed as part of the written consent, the Working Group agrees with NBAC's suggestion that this topic be accorded special attention.

The Working Group cautions, however, that the terms "clinical settings" and "quality of their clinical care" in the recommendation may mean different things to different people. "Clinical settings" could refer to settings that house routine clinical care, clinical research, or both. It is important that those who are responsible for obtaining consent from potential research subjects be mindful of this fact. The use of the words "clinical care" preceded by "quality" makes the phrase "quality of their clinical care" susceptible to misinterpretation by patients. To state that declining to participate in research "will in no way affect the quality of their clinical care" does not recognize the fact that, as a result of participating in research, some research participants may have access to care procedures that are not generally available. Saying "no" to a request to collect and study human biological materials may restrict an individual's access to care provided as part of a research study but should not unfavorably impact an individual's routine clinical care.

## Proposed Actions

1. The Working Group proposes that OHRP, in consultation with FDA, reinforce to research institutions that individuals who are responsible for obtaining informed consent should be provided with training that emphasizes the approaches, techniques and sensitivities that are essential to implementing this recommendation.
2. The Working Group proposes that this recommendation guide the development of consent forms and be addressed in the workshop proposed as part of DHHS response to Recommendation 6.

Recommendation 8. *When an investigator is conducting research on coded or identified samples obtained prior to the implementation of NBAC's recommendations, general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time. Investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. If the existing documents are inadequate and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped so that samples are unlinked.*

## Discussion

In general, the Working Group agrees with Recommendation 8, although there are some practical issues could complicate implementation. The Working Group applauds NBAC's recognition that much research on human biological materials is of minimal risk and therefore potentially eligible for a waiver of consent.

The Working Group agrees wholeheartedly with the first part of Recommendation 8, which indicates that, simply because a consent form for one kind of research was signed, it cannot be assumed that the consent is applicable to all types of research for an indefinite period of time. Conversely, in the absence of specific limitations or restrictions on sample use, the absence of consent for activities not envisioned at the time a sample was collected cannot be presumed to mean that consent would have been denied for the proposed research. The Working Group believes therefore that each case must be judged on its own merits.

The Working Group concurs in principle with the second part of Recommendation 8, which states that "investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed."<sup>24</sup> Furthermore, the Working Group suggests adding repositories to the list of parties that should be responsible for reviewing the consent documents, where such documents are available to the repository. The Working Group notes that the repository's review of consent forms is especially important when the repository will anonymize samples before sending them to the researcher. In such cases, the repository may be the only party in a position to honor limits placed on research use of any given sample. The Working Group expects, however, that the

majority of archived human biological materials will not be accompanied by any informed consent documents. For example, consents may have been misplaced over time or may be embedded in medical records held by a separate clinical facility. In situations where consents are available, institutions, IRBs and repositories will need guidance and training to institute best practices for evaluating the adequacy of consent documents.

The Working Group also concurs with the third part of this recommendation, which addresses the situation where consent is unavailable or inadequate to determine the wishes of the sample source with respect to the proposed research. NBAC proposed three conditions, any of which, if satisfied, would permit such research:

- a) waiver of consent from an IRB; or
- b) obtaining informed consent from subjects; or
- c) unlinking/anonymizing samples.

IRBs, researchers and repositories will need new guidance in order to implement this recommendation. Guidance is needed both to assess whether previous consent is adequate to permit research that had not been envisioned at the time of sample collection as well as to evaluate the level of risk in the newly proposed research.

#### Proposed Action

The Working Group proposes that OHRP, in consultation with relevant DHHS agencies and appropriate stakeholders, take the lead in developing guidance for researchers, IRBs and repositories on evaluating the adequacy of extant consent documents for proposed use of existing human biological samples in research. In those cases in which consent is either not adequate or unavailable, the guidance should emphasize that the investigator may proceed only if he/she has met one of the three conditions set forth in this recommendation.

Recommendation 9. *To facilitate collection, storage, and appropriate use of human biological materials in the future, consent forms should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make. Such options might include, for example:*

- a) *refusing use of their biological materials in research,*
- b) *permitting only unidentified or unlinked use of their biological materials in research,*
- c) *permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies,*
- d) *permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies,*
- e) *permitting coded or identified use of their biological materials for any study relating to*

*the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, or*

*f) permitting coded use of their biological materials for any kind of future study*

## Discussion

The Working Group concurs with Recommendation 9 and commends NBAC for having formulated this recommendation to include a variety of *examples* (emphasis added) of conditions under which a subject's human biological materials may be used. This flexibility allows for the development of consent forms that vary in the number and types of options that are included, depending upon the nature and objectives of the study.

The Working Group agrees that additional efforts need to be made to develop appropriate consent forms. NBAC refers to work done by "NIH and advocacy groups such as the National Action Plan for Breast Cancer" on "designing multilayered consent forms that are both informative and practical."<sup>25</sup> Practical issues to consider in implementation include requirements for personnel and time, the need to ensure that pertinent information from the consent forms accompanies the samples, and the ability of researchers and repositories to understand and comply with the wishes of the sample sources in the years to come. Further study is needed to assess the impact that the number and type of options in a consent form will have on the ability of a potential subject to understand the options and on the researchers' ability to carry out important research. NBAC concludes, and the Working Group agrees, that efforts to design and use improved consent forms "should be encouraged and continued."<sup>26</sup>

DHHS, through various agencies and offices, is actively working to improve the consent process in ways that directly address NBAC's recommendation. As previously noted, NIH, in collaboration with CDC, is currently funding 18 research projects addressing informed consent. This program includes a feature to encourage interaction among researchers and a strategy to translate research results to practice. A component of the National Institute of Allergy and Infectious Diseases has disseminated to investigators an informed consent template that addresses future use of human biological materials. For intramural NIH researchers, the NIH Office of Human Subject Research posted on its website revised guidance on informed consent for the use of human biological materials.<sup>27</sup> HRSA is funding the development of model policies for informed consent for storage and research use of samples collected from newborn screening programs. The CDC guide to writing informed consent documents, which includes examples of good practices, is currently being revised to include information directly relevant to NBAC's Recommendation 9.<sup>28</sup> IHS is developing and will post on its website a new model consent form that will specifically address issues raised by Recommendation 9.<sup>29</sup> Finally, OHRP plans to revise Chapter 5 (Human Genetics Research) of the IRB Guidebook, which contains guidance pertinent to this recommendation.

## Proposed Actions

1. The Working Group proposes that DHHS agencies continue funding studies in this area and

that findings from such studies be made available to researchers and IRBs.

2. The Working Group proposes that the workshop on informed consent, proposed as part of the DHHS response to Recommendation 6, also address issues related to the development and use of layered consent forms with multiple options.

### **Recommendations Regarding the Criteria for Waiver of Consent**

Recommendation 10. *IRBs should operate on the presumption that research on coded samples is of minimal risk to the human subject if*

- a) *the study adequately protects the confidentiality of personally identifiable information obtained in the course of research,*
- b) *the study does not involve the inappropriate release of information to third parties, and*
- c) *the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure.*

Recommendation 11. *In determining whether a waiver of consent would adversely affect subjects' rights and welfare, IRBs should be certain to consider*

- a) *whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality,*
- b) *whether the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects, and*
- c) *whether the study's results might adversely affect the welfare of the subject's community.*

Recommendation 12. *If research using coded or identified human biological materials is determined to present minimal risk, IRBs may presume that it would be impracticable to meet the consent requirement (45 CFR 46.116(d)(3)). This interpretation of the regulations applies only to the use of human biological materials collected before the adoption of the recommendations contained in this report (specifically Recommendations 6 through 9 regarding informed consent). Materials collected after that point must be obtained according to the recommended informed consent process and, therefore, IRBs should apply their usual standards for the practicability requirement.*

Recommendation 13. *OPRR should make clear to investigators and IRBs that the fourth criterion for waiver, that "whenever appropriate, the subjects will be provided with additional pertinent information after participation" (45 CFR 46.116(d)(4)), usually does not apply to research using human biological materials.*

## Discussion

Collectively, recommendations 10, 11, 12 and 13 address the four criteria set forth in 45 CFR 46.116(d) under which a waiver of consent may be granted. The Working Group agrees in principle with these four recommendations and finds that they clarify and simplify the process by which IRBs can determine whether or not to grant a waiver of consent for research involving human biological materials. In addition, the Working Group agrees that these four recommendations provide a logical, sensible, and appropriately flexible approach to interpreting and applying the existing criteria for waiver of consent to research. Since all four criteria must be satisfied before a waiver of consent is granted, the Working Group elected to consider these four recommendations as a group.

The Working Group emphasizes that the criteria for waiver of informed consent for research undertaken under FDA regulations differ from those described in 45 CFR 46.116(d). FDA's regulations 21 CFR 50.23 and 50.24 permit a waiver of informed consent only in very limited circumstances.<sup>30</sup>

There are two issues that appear throughout the discussion of these four recommendations and require explanation here. First, disclosure of research results to subjects may involve either information pertinent to an individual or general information that does not relate specifically to an identifiable individual. For clarity, the Working Group refers to research results that pertain to an individual as "individual research results." Second, the Working Group distinguishes between disclosure of research results that is initiated by the researcher, who offers unsolicited information to a subject, and the disclosure of results in response to a direct request from the study subject.

### Recommendation 10

The first criterion to be met for granting a waiver of consent is that subjects should not be exposed to more than minimal risk. Recommendation 10 addresses this criterion, focusing specifically on individually identifiable information. The Working Group agrees that this is the most critical issue for determination of minimal risk in studies that involve human biological materials. The Working Group agrees with Recommendation 10 (a) and (b) that a study using appropriate strategies to protect such information may be presumed to be of minimal risk.

The Working Group is persuaded that studies for which consent can be waived will generally be those for which it is not expected that research results will merit disclosure to subjects. The Working Group appreciates the caution and sensitivity signaled by NBAC in 10(c) with respect to the possibility that individual research results may be so compelling that the investigator may feel obligated to initiate disclosure of such findings even when such disclosure had previously been considered unlikely. In certain types of research, the likelihood is small that research findings could be so significant as to merit investigator-initiated disclosure to an individual who is not aware of having been a study subject. For some of these studies, it will be difficult to predict what kind of results might merit such disclosure. Consequently, it will be difficult for the researcher to develop - and for the IRB to assess - an appropriate plan for whether and how

to disclose results. For such studies, the researcher could make a commitment that (1) if individual research results appear to merit disclosure, the researcher would then develop and submit for IRB approval a disclosure plan, and (2) no investigator-initiated disclosure would take place until IRB approval was granted. For other studies for which it may be feasible to predict results that might merit disclosure, the investigator should develop an appropriate plan for such a contingency at the time of the initial IRB review. When it is unlikely that results will merit disclosure and when there is an appropriate plan in place to address that unlikely event, the proposal would be eligible for a waiver of consent. In sum, the Working group agrees with NBAC that a high threshold should be applied when determining whether an investigator should offer individual research results to a subject of a study conducted under a waiver of consent.

The Working Group also appreciates NBAC's suggestion that the researcher may work through the subject's physician to offer unsolicited research results to the subject. However, involving the study subject's health care provider is not a substitution for the IRB's responsibility to determine whether the value of disclosing results outweighs risk of such disclosure. In addition, the Working Group cautions that most health care providers are not trained to critically evaluate all relevant aspects of research findings. Health care providers who are asked to provide their patients with unexpected information will need education and support regarding best approaches for disclosure, including approaches to maximize potential benefit to the study subject and minimize damage to the ongoing relationship between health care provider and patient.

#### Recommendation 11

The second criterion for waiver of consent emphasizes that consent may not be waived if such action would adversely affect subjects' rights and welfare.

Recommendation 11(a) refers to the question of whether a waiver of consent for a proposed study might violate any federal or applicable state statutes or customary practices regarding entitlement to privacy or confidentiality. Current DHHS regulations (45 CFR 46.107(a)), supported by existing guidance,<sup>31</sup> require IRBs to be knowledgeable about relevant statutes and practices. In addition, 45 CFR 46.116 (d) (2) does not allow an IRB to grant a waiver of consent if the proposed research would adversely affect the study subjects' rights.<sup>32</sup> Application of recommendation 11(a) therefore requires a factual response: granting a waiver of consent for the proposed study either violates or does not violate state or federal laws regarding entitlement to privacy or confidentiality. If it does, a waiver of consent may not be granted.

The Working Group believes that 11(b) and (c) should be regarded as conditions that will require a higher level of scrutiny of a proposal by the IRB but which, even if they existed in a given research proposal, do not preclude granting of a waiver of consent. As long as the IRB determines that a study examining traits considered to have political, cultural or economic significance to the study subjects does not adversely affect the subjects' rights and welfare, such a study should be eligible for a waiver of consent. Finally, in 11(c) NBAC focuses on the risk that a study might adversely affect the welfare of a subject's community. Federal regulations

governing waiver of consent address the rights and welfare of the *individual* (emphasis added) study subject. The IRB would therefore need to consider whether, if there were reason to believe that a study could cause harm to a group, such group harm would also adversely affect the rights and welfare of individual study subjects. The Working Group notes that the subject of group harm is addressed more fully in Recommendations 18 and 19.

#### Recommendation 12

Recommendation 12 addresses the question of whether or not it is impracticable to obtain consent for research. While the Working Group believes that on occasion it may be practical to obtain consent for new uses of existing samples, the Working Group also agrees that in most cases it is impracticable. Thus, the Working Group agrees in principle with Recommendation 12 and considers it a reasonable approach to interpreting 45 CFR 46.116(d)(3) in a manner that is consonant with the principle of protecting human subjects while allowing investigators access to existing human biological materials. However, the Working Group is concerned about NBAC's suggestion on implementation of this recommendation at a specific point in time.

Use of improved strategies for obtaining informed consent before collecting human biological samples (such as those in Recommendations 6-9) does not guarantee that, in the future, subjects' wishes regarding new uses of existing samples will always be unequivocal. In addition, the Working Group notes that currently some IRBs do not consider the procedural or financial burdens associated with seeking consent to be evidence of impracticability; instead, they require proof that it is impossible to contact subjects before granting a waiver of consent. The Working Group shares NBAC's concern that some IRBs may set an unrealistically high threshold for determining whether or not it is impracticable to seek consent. The Working Group believes that IRBs need additional guidance regarding definition of impracticability to clarify the conditions under which presumption of impracticability may be made. Such guidance would also address the issue of when and how the definition should be applied.

#### Recommendation 13

Recommendation 13 recognizes that the fourth criterion under which a waiver of consent may be granted will usually not be applicable to research involving human biological materials. The Working Group notes that NBAC's conclusion is consistent with the history and original purpose of the fourth criterion for waiver of consent. 45 CFR 46.116(d)(4) is particularly important for certain types of behavioral research in which the research results would be invalid if subjects knew that they were being studied and in which subjects are informed of their participation and the results following completion of the research.

The Working Group notes that a research project that meets the third criterion for waiver of consent (45 CFR 46.116(d)(3), addressed in Recommendation 12) is one in which it is impractical to contact subjects for consent. Therefore, one could argue that it would be equally impractical to contact subjects to provide information. This does not, however, preclude an investigator from attempting, as provided for in NBAC's recommendation 10(c), to contact subjects in order to offer information, in the event that individual research results merit

disclosure. In addition, notwithstanding the Working Group's agreement with Recommendation 13, subjects have a right to request and receive information about themselves. This issue is addressed further in the response to Recommendation 14.

### Proposed Action for Recommendations 10-13

The Working Group proposes that OHRP, in consultation with relevant DHHS agencies and appropriate stakeholders, prepare and disseminate guidance to support implementation of Recommendations 10-13.

### **Recommendations Regarding Reporting Research Results to Subjects**

Recommendation 14. *IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address these issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following apply:*

- a) the findings are scientifically valid and confirmed,*
- b) the findings have significant implications for the subject's health concerns, and*
- c) a course of action to ameliorate or treat these concerns is readily available.*

### Discussion

As noted in the Working Group's response to Recommendations 10-13, it is important to distinguish between investigator-initiated disclosure of individual research results and disclosure of such results in response to a request from a study subject. While the discussion that prefaces NBAC's Recommendation 14 contains references that pertain to either or both types of disclosure, the Recommendation itself does not draw a distinction. In considering the implementation of Recommendation 14, the Working Group considered both types of disclosure.

#### The Privacy Act and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Regulation

With respect to study subjects who desire access to their individual research results, Recommendation 14 appears to be in conflict with both the Privacy Act and provisions of the HIPAA privacy rule.

The Privacy Act, passed in 1974, applies to certain personally identifiable information held by federal agencies in a "system of records" and thus applies to any research record held by DHHS. Under this law, an agency must provide an individual access to his or her record. Moreover, the rules for protection of human subjects prohibit consent forms from including

language “through which the subject or his representative is made to waive or appear to waive any of the subject’s legal rights” (45 CFR 46.116).

As interest has grown in protecting an individual’s access to his/her personal information, federal agencies are taking additional steps to ensure compliance with the Privacy Act. For example, as of March 1999, new consent forms at the NIH Clinical Center must include a statement that subjects have not waived their right to access to records about themselves. This statement must appear in consent forms for studies in which subjects are informed that the researcher does not plan to initiate disclosure of research results to study participants.

The HIPAA privacy regulation applies to health care providers who engage in certain electronic transactions. Therefore, any researcher who provides health care to research participants as part of a study, and engages in the specified electronic transactions, is covered by the regulations. It is expected that the HIPAA privacy regulation will apply to virtually all providers who conduct clinical trials. The HIPAA privacy regulation not only gives patients a right to see their own records but also requires that patients be notified of their right to see such records. None of the few exceptions in the HIPAA privacy regulation appear to apply to the situation envisioned by Recommendation 14. While its applicability to research in which health care is not provided (e.g., studies based solely on tissue samples with no clinical care component) is not entirely clear, the general rule of patient access to records may become an expected feature of the delivery of health care. Once health care facilities implement the HIPAA privacy regulation (in 2003), it is likely that subjects’ requests for access to their research results will no longer be an exceptional circumstance. The Working Group believes that such a regulatory requirement is most likely to lead to an increase in the number of subjects who are aware of and exercise their right to request and receive research results, all of which will have resource implications for the researcher. Investigators will have to be prepared to include, and IRBs to review, plans for how to respond to subjects’ requests for disclosure of research findings.

The HIPAA privacy rule is complex, and implementation will be a lengthy process. The impact of the new privacy regulations on research, including disclosure of research findings to participants will not be known for several years. The Working Group concludes that further analysis is needed before DHHS can make any judgment regarding the legality and feasibility of implementing Recommendation 14.

#### Conditions for disclosure of research results

The following comments relate in principle to both investigator-initiated disclosure and disclosure in response to a subject’s request. However, it is important to remember that under the HIPAA privacy regulation and the Privacy Act, a subject’s request for release of research results must be honored by an entity that is required to comply with either the HIPAA privacy regulation or the Privacy Act.

The Working Group agrees with NBAC that there are two major principles that need to be weighed when considering disclosure of research results to subjects:

- < information that is preliminary and unvalidated could raise unnecessary concerns and/or lead to imprudent or inappropriate action by subjects
- < subjects have the right to know what a researcher has found out about them and decide for themselves what is “significant” and what is not

Keeping these potentially conflicting principles in mind, the Working Group considered each of the three conditions in Recommendation 14 that would need to be satisfied before disclosure is permitted.

In general, the Working Group agrees with the principles in Recommendation 14(a), since results of research do not necessarily constitute valid information. However, the Working Group believes that the definition of “scientifically valid” may need further clarification with respect to issues such as clinical validity, clinical utility, and the variability of such measures across different study populations. Furthermore, during the course of investigations involving human biological materials, unforeseen information or circumstances may come to light that pose serious concerns for the safety of the subjects, individuals in contact with them, or even the public at large. In many such cases, the information will be preliminary, unvalidated, or unverified; but timely action may nevertheless be imperative.

The Working Group is troubled by the implication that failure to meet the conditions in either Recommendation 14(b) or 14(c) would always preclude investigator-initiated release of research results even when such results are valid. The Working Group is persuaded that individuals have differing personal perspectives about whether information has “significant implications” for their own health and questions whether an IRB or investigator is necessarily qualified to make such judgments on behalf of the subject. Furthermore, even if there is no prevention or treatment measure that the researcher or IRB judges to be effective, having this information may allow the subject to make certain life choices or to engage in an intervention or additional research that the subject believes may be helpful. In other cases, although no useful medical options may be available to the subject from whom the biological material was collected, interventions to protect close contacts and health care workers may be appropriate. In any such scenario, subjects will be best served if the investigator initiates disclosure of valid results. This would be far preferable to dissemination of such information to subjects via the mass media.

The Working Group is aware that reluctance on the part of investigators to disclose research results to subjects often reflects the researcher’s concern about misuse of preliminary and unvalidated research data and the potential harm that may result from inappropriate actions. Researchers must, however, be prepared to respond to subjects’ requests for preliminary or unvalidated research results. Every effort should be made to ensure that information is released in a manner that would minimize harm and maximize benefit to the subject. The need to

explain concerns about the findings and to promote caution in interpreting research results will place a further burden on the time and resources of investigators.

### Proposed Action

The Working Group proposes that a separate working group be convened to analyze the potential conflicts between this NBAC recommendation and HIPAA privacy regulation and to propose an appropriate Departmental response. The new working group should be drawn from not only staff involved in overseeing human biological materials research but also staff who are knowledgeable about the DHHS privacy regulation and federal clinical laboratory regulations. Moreover, the new working group should take into consideration the views of this Working Group on Recommendation 14, especially with respect to the conditions for disclosure.

Recommendation 15. *The investigator in his or her research protocol should describe anticipated research findings and circumstances that might lead to a decision to disclose the findings to a subject, as well as a plan for how to manage such a disclosure.*

### Discussion

The Working Group concurs with Recommendation 15. The protocol submitted for IRB review should (1) address any foreseeable circumstances that might lead the investigator to conclude that individual research findings should be disclosed to a subject and (2) include a plan that describes how subjects might be contacted to share such results.

Recommendation 15 is similar to Recommendation 10(c), which entertains the possibility of disclosing individual research results to subjects when such results merit investigator-initiated disclosure to an individual who was not aware of having been a study subject. Having recommended that OHRP, in consultation with FDA, develop and disseminate guidance to implement Recommendations 10-13, including 10(c), the Working Group proposes that the guidance developed for Recommendation 10(c) be formulated in a manner that is also responsive to Recommendation 15.

### Proposed Action

The Working Group proposes that OHRP, in consultation with relevant DHHS agencies and appropriate stakeholders, develop and disseminate guidance to implement this Recommendation, in conjunction with guidance for implementation of Recommendations 10-13.

Recommendation 16. *When research results are disclosed to a subject, appropriate medical advice or referral should be provided.*

### Discussion

The Working Group concurs with Recommendation 16 and interprets it as applicable to either disclosure initiated by the investigator or in response to a subject's request. Disclosure of research results to a subject should include such information as is necessary for the subject to understand the potential implications of the information and the options available to address any

health consequences. When appropriate, a plan for disclosure of individual research results to a subject would include a description for how advice or referral would be provided. Institutions, investigators, health care providers and community health advocacy groups could collaborate to identify sources of relevant information, including individuals or groups to whom a subject could be referred, that would be made available to researchers who foresee the possibility of disclosing research results to study subjects. Often, however, only the investigators will be qualified to provide the information that subjects need to understand the implications of the research results; and additional resources may be required to support the personnel, time and effort needed to provide such information.

### Proposed Action

The Working Group proposes that issues relevant to implementation of this recommendation be included in guidance to be developed for implementation of Recommendations 10(c) and 15.

### **Recommendations Regarding the Considerations of Potential Harms to Others**

Recommendation 17. *Research using stored human biological materials, even when not potentially harmful to individuals from whom the samples are taken, may be potentially harmful to groups associated with the individual. To the extent such potential harms can be anticipated, investigators should, to the extent possible, plan their research so as to minimize such harm and should consult, when appropriate, representatives of the relevant groups regarding study design. In addition, when research on unlinked samples that poses a significant risk of group harms is otherwise eligible for exemption from IRB review, the exemption should not be granted if IRB review might help the investigator to design the study in such a way as to avoid those harms.*

### Discussion

The Working Group shares NBAC's concern that some research using human biological materials may be potentially harmful to groups. However, as NBAC points out, "federal regulations governing the protection of research subjects extend only to individuals who can be identified."<sup>33</sup> Thus, the regulations do not include federal oversight of research that may pose risk of group harm (beyond the risks to study participants who are members of the group) except insofar as the requirements for IRB membership provide some protection for vulnerable groups.

Notwithstanding the silence of federal regulations on this point, the Working Group agrees that investigators should plan research in a manner that minimizes potential harm to groups. Consultation with representatives of relevant groups may identify potential harms and other problems as well as benefits and opportunities in the proposed research that may not have been evident to the investigator. Appropriate consultation may thus minimize harms, maximize benefits, and increase the likelihood that the research will be carried out successfully.

However, as NBAC notes, "additional work is needed to identify appropriate mechanisms for

group consultation.”<sup>34</sup> Identifying the appropriate groups to consult with may, in certain instances, be a complex challenge. The researcher may identify and consult with a group regarding the proposed research only to find that another or larger group claims that the originally defined group is in fact a sub-group whose views do not reflect those of the larger group. This larger group may disagree with, and even claim the authority to override, the decision of the initial group.

A group could be an informal collection of individuals, a formal organization with identified leadership, or include competing organizations with dissimilar opinions. Therefore, even when a group is identified, individuals or sub-groups within a group may have different opinions about the relative risk and value of the proposed research, who will be affected by the results, and the best research design for the study. Furthermore, some groups explicitly authorize only certain members to determine and express group opinion. These issues all contribute to the difficulty the researcher will experience in efforts to identify appropriate formal and informal spokespersons for a group. This uncertainty about how best to conduct group consultation militates against proposing a regulatory requirement in the near future.

Nevertheless, DHHS agencies are making efforts that are in keeping with the spirit of NBAC’s call for improvement of mechanisms for group consultation. For example, NIH convened in September 2000 a community consultation to obtain input on the collection of tissue samples from members of identified populations; the results of this consultation are posted on the internet.<sup>35</sup>

In the discussion preceding Recommendation 17, NBAC points out that, for many studies involving human biological samples, the “net gain to a particular population that results from being informed about its increased risk (especially when something can be done with this knowledge at an individual level) often will outweigh the harms that come from labeling the group as high risk.”<sup>36</sup> In the United States, with one exception,<sup>37</sup> consultation with representatives of a group does not confer the right of veto over the research to those representatives. Nonetheless, bona fide consultation requires the researcher and the IRB to carefully consider the concerns, especially the perceived potential harms, of the group and of individuals in that group. If those potential harms cannot be sufficiently minimized, it is possible that the benefit to risk assessment may require that consideration be given to not proceeding with the research.

Under 45 CFR 46.101(b)(4) and 102(f), research on unlinked or anonymized samples is not subject to the Regulations. Individual institutions and IRBs have the authority to apply a more stringent standard than that required by the Regulations. Within an institution, an IRB may require that a proposal be submitted for review even if the proposal is otherwise not subject to federal regulations. The Working Group strongly encourages efforts to minimize group harm in all research, even research that is not subject to federal regulations. In this context, the Working Group encourages IRBs and institutions to consider risk of group harm in research involving unlinked or anonymized samples and to develop strategies to minimize such risk. However, absent revision to the Regulations, IRB review of proposals to which current federal regulations do not apply is not mandated.

### Proposed Action

The Working Group proposes that the issue of group harm be addressed in the broader context of federal oversight of research involving humans that is being addressed in NBAC's forthcoming report on *Ethical and Policy Issues in Research Involving Human Participants*. In the interim, the Working Group suggests that DHHS continue to encourage further studies of strategies that would identify and effectively minimize group harm, including efforts to identify appropriate mechanisms for consultation with relevant groups.

**Recommendation 18.** *If it is anticipated that a specific research protocol poses a risk to a specific group, this risk should be disclosed during any required informed consent process.*

### Discussion

The Working Group agrees that disclosure of foreseeable risk to groups should be included in the informed consent process. Potential subjects should have access to all information that could affect their decisions about participation. Individuals may wish to consider implications of the research design and/or results for their community in deciding whether or not to participate in a research study.

### Proposed action

The Working Group proposes that OHRP, in consultation with FDA, consult with appropriate groups and organizations to develop guidance for implementation of this recommendation.

## **Recommendations Regarding the Publication and Dissemination of Research Results**

**Recommendation 19.** *Investigators' plans for disseminating results of research on human biological materials should include, when appropriate, provisions to minimize the potential harms to individuals or associated groups.*

### Discussion

The Working Group concurs with this recommendation. In language accompanying Recommendation 19, NBAC highlights the need to consider the risk of violating privacy rights when publishing written descriptions of patients, pedigrees, and other clinical or potentially identifying information about individuals, families, and associated groups. Some of these concerns are addressed in OHRP's Institutional Review Board Guidebook, Chapter 5 H (Human Genetic Research).

It is difficult to guarantee protection against identification of subjects, especially when publishing about an unusual or rare condition or about people from small groups. Strategies have been developed to reduce that risk, however, especially for presentation of pedigrees in the literature.

While it is difficult to ensure compliance with this recommendation, the Working Group believes that education of investigators regarding best practices can reduce risk to study subjects. It has also been noted that published materials do not always conform with professional editorial standards, such as those established by the International Committee of Medical Journal Editors in 1995.<sup>38</sup> Journal editors should therefore be mindful of the role that they can play in minimizing potential harm to individuals and to groups when publishing results. Finally, members of a small geographic or ethnic group or of a family can sometimes help the researcher more effectively mask individual or group identities and thus minimize the risk of disclosure.<sup>39</sup>

#### Proposed Action

No DHHS action is required.

Recommendation 20. *Journals should adopt the policy that the published results of research studies involving human subjects must specify whether the research was conducted in compliance with the requirements of the Common rule. This policy should extend to all human subjects research, including studies that are privately funded or are otherwise exempt from these requirements.*

#### Discussion

The Working Group concurs with this recommendation, which is directed at journals and editorial boards. A statement indicating investigator compliance with federal human subject protection regulations will serve as a visible reminder to both researchers and journal editors of their ethical obligations with respect to the conduct and publication of research involving human subjects. Consistent editorial policies across all publications with respect to this issue will also serve to increase the likelihood that future studies, regardless of funding source, will be conducted in accord with the standards set forth in the Regulations.

#### Proposed Action

No DHHS action is required.

### **Recommendation Regarding Professional Education and Responsibilities**

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

#### Discussion

The Working Group supports NBAC's goal but feels that Recommendation 21 is too narrowly

focused, both with respect to identification of those responsible for providing education and training and with respect to those in need of education.

Recommendation 21 identifies the NIH as having a responsibility to train investigators about ethical issues and regulations that are relevant to research on human biologic materials. Other DHHS agencies, including CDC, FDA, HRSA and IHS, also conduct, support or regulate research on human biologic materials and engage in activities relevant to implementation of NBAC's recommendation. In fact, several of these DHHS agencies are already implementing programs and policies that are consistent with the intent of NBAC's recommendation. Furthermore, there are other federal departments, for example USDA, DoD and DoE, that also conduct and support research involving human participants. These departments should also be partners in the educational efforts that NBAC describes.

As part of the DHHS initiative to further enhance protections for human research subjects, as of October 1, 2000, NIH requires that all NIH-sponsored clinical investigators working with human subjects receive appropriate research bioethics and human subjects research training as a condition of their NIH grant award<sup>40</sup>. To assist researchers in determining whether the research they are conducting with human specimens is human subjects research, the NIH has developed a user-friendly brochure to help investigators understand how 45 CFR Part 46 applies to their research.<sup>41</sup>

#### Proposed Action

The Working Group proposes that, in addition to ongoing and separate endeavors by DHHS agencies and offices, efforts be made to coordinate education and training related to research with human biological materials in order to avoid duplication of efforts and to maximize the impact of available resources.

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

#### Discussion

Recent attention to instances of inadequate protections for human research subjects and several reports prepared by the DHHS Inspector General have spotlighted weaknesses in the infrastructure for protection of human subjects in federally supported research. Some of these weaknesses have been attributed to the lack of adequate resources. NBAC recognizes that implementation of the recommendations in its report on research involving human biological materials will require additional resources – for enhanced federal oversight, for development of appropriate guidance materials, for institutions and IRBs, for researchers, for convening of workshops, and for educational efforts. The Working Group recognizes the merit of Recommendation 22 and notes not only the need for new resources but also the need to ensure appropriate utilization of existing resources.

### Proposed Action

The Working Group proposes that DHHS continue to work with awardee institutions to highlight the importance of adequate support for IRBs and for other appropriate human subjects protection measures.

### **Recommendation Regarding the Use of Medical Records in Research on Human Biological Materials**

*Recommendation 23. Because many of the same issues arise in the context of research on both medical records and human biological materials, when drafting medical records privacy laws, state and federal legislation should seek to harmonize rules governing both types of research. Such legislation, while seeking to protect patient confidentiality and autonomy, should also ensure that appropriate access for legitimate research purposes is maintained.*

### Discussion

The Working Group agrees with Recommendation 23. While there is significant similarity and overlap between research involving human biological materials and research involving medical records, there are also important differences between these two types of research. Analysis is necessary to determine how best to harmonize laws and regulations governing both types of research in order to ensure adequate and equal protection in a fair and practical manner. Although this recommendation is addressed to Congress and to state legislatures, DHHS is actively involved in efforts to improve health records privacy and can serve as a resource to those at the state level who will be drafting such health privacy laws and regulations.

### Proposed Action

No DHHS action is required.

## END NOTES

1. NBAC Report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* at, for example, pages 57, 58, 59 and 61.
2. Widely varying definitions for “genetic testing” and “genetic information” have been proposed and/or adopted by professional associations and advisory committees, in legislation, and in regulations. The charge to the Working Group did not include a mandate to define these terms. The Working Group acknowledges that these differences in definition will need to be resolved jointly by the relevant federal agencies, the scientific community (including the Secretary’s Advisory Committee on Genetic Testing), the public, and industry.
3. Ibid. at page 59.
4. OPRR Report #95-02 provides guidance for carrying out this responsibility and explicitly states that a researcher cannot be the final arbiter of whether or not his or her research is subject to the Regulations. The report can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hcdc95-02.htm>
5. Relevant current guidance:
  - < “Engagement of Institutions in Research” (January 26, 1999) can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm>
  - < “Human Subject Regulations Decision Charts” (October 1, 1998) can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/decisioncharts.htm> and
  - < “Issues to Consider in Research Use of Stored Data or Tissues” (November 7, 1997) can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm> (note particularly the last page, dated May 22, 1997 and titled "Submission of Non-identifiable Materials to the Repository.")
6. NBAC Report at page 60.
7. Ibid. at page 61.
8. When therapeutic products are manufactured from human cells or tissue, safety of the recipient becomes the overriding concern. In sharp contrast to the issues posed by concerns for donor confidentiality, extensive experience has demonstrated repeatedly that inadequate knowledge of biological source materials can be life-threatening. The two primary concerns are: (a) microbiological safety testing will not necessarily identify all pathogens; and (b) donor characteristics that are not understood at present may prove to exert decisive effects on the clinical outcome. Thus, the ability to reexamine issues related to donor characteristics may prove crucial to treatment of unexpected adverse effects in biological materials recipients as well as continued scientific progress.
9. NBAC Report at page 61.
10. The Working Group notes that the process of certifying that research is not covered by the Regulations does not generally involve the broad array of expertise necessary to (1) judge the expected value of the proposed study (using anonymized samples), (2) assess the expected value of the same study if conducted with identifiable samples, and (3) draw conclusions about whether the difference in expected value is justified. The Working Group believes that such determination of comparative scientific value should remain within the purview of scientific merit review bodies.
11. Relevant current guidance:
  - < “Operation of Human Cell Repositories Under HHS Regulations at 45 CFR 46” (August 19, 1996) and

“Issues to Consider in the Research Use of Stored Data or Tissues”(November 7, 1997) can both be found at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm>

< “Engagement of Institutions in Research,” (January 26, 1999) can be found at: <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm>

12. The Institutional Review Board Guidebook, Chapter 3(a) “Risk Benefit Analysis” can be found at: [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm#e1](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm#e1)

13. The Institutional Review Board Guidebook, Chapter 3(d) “Privacy and Confidentiality” can be found at: [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter3.htm#e4](http://ohrp.osophs.dhhs.gov/irb/irb_chapter3.htm#e4)

14. The Institutional Review Board Guidebook, Chapter 4 “Considerations of Research Design” can be found at: [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter4.htm](http://ohrp.osophs.dhhs.gov/irb/irb_chapter4.htm)

15. The Institutional Review Board Guidebook, Chapter 5(h) “Human Genetic Research” can be found at: [http://ohrp.osophs.dhhs.gov/irb/irb\\_chapter5ii.htm#h12](http://ohrp.osophs.dhhs.gov/irb/irb_chapter5ii.htm#h12)

16. Memorandum titled “IRB Knowledge of Local Research Context” (August 27, 1998, updated July 21, 2000) can be found at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm>

17. Certificates of confidentiality is addressed in “Privacy Protection for Research Subjects”, which can be found at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/certconpriv.htm>

18. NBAC Report at page 64.

19. In 1997, NIH issued a Request For Applications (RFA) soliciting proposals to study the informed consent process, and funded 18 of the applications received in response to the RFA. The third meeting of these NIH supported investigators was held in April, 2000, and the researchers are collaborating on a joint report of the research results. In addition, in 1999 a Program Announcement (PA) titled “Research on Ethical Issues in Human Studies” was published in the NIH Guide for Grants and Contracts (<http://grants.nih.gov/grants/guide/pa-files/PA-99-079.html>). This PA, supported by 20 Institutes and Centers of the NIH and by the CDC, is intended to support research on any topic relevant to ethical issues in research, including studies focusing on conditions under which consent is obtained. To date, four applications have been funded under this PA. A condition of funding is participation in yearly meetings to report progress, discuss problems and share information with other investigators funded under the Program.

20. Results of the study, funded by NCI, are currently being analyzed. The investigators examined the use of the National Action Plan for Breast Cancer model consent form in the clinical setting. The study is designed to evaluate whether prospective subjects accept the format, whether information included in the consent form is retained, and what staff and fiscal resources are required for using this model form for obtaining consent in the clinical setting. Preliminary results indicate that information in the consent form was understood and retained, and that obtaining informed consent using this model requires additional time and may possibly require dedicated personnel. The study also raises questions about tracking consents, once samples are stored, in order to ensure compliance with the wishes of the sample sources and about processes and procedures to be used if and when a subject wishes to withdraw consent.

21. NBAC Report at page 64.

22. The “Informed Consent Checklist” (Sept 30, 1998) can be found at: <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/consentckls.htm>

23. Additional relevant materials are contained in the FDA Information Sheets for IRBs and Clinical Investigators. In particular the sheet "A Guide to Informed Consent", which can be found at <http://www.fda.gov/oc/oha/IRB/toc5.html>, contains guidance on the meaning of 21 CFR 50.25(a)(8).
24. NBAC Report at page 64.
25. Ibid. at page 66.
26. Ibid.
27. "Points to Consider in Development of Informed Consent Documents that Include the Collection and Research Use of Human Biological Materials" (Information Sheet #15, revised August 2000) from the Office of Human Subject Research (OHSR) at NIH can be found at: [http://ohsr.od.nih.gov/info/oinfo\\_15.php3](http://ohsr.od.nih.gov/info/oinfo_15.php3)
28. Pages 43-46 of the current version of the CDC guide to writing informed consent documents specifically addresses options that may be appropriate to include in consent documents when requesting permission to store human biological materials for future research. The document is found at: <http://www.cdc.gov/od/ads/consent.pdf>
29. Sample consent forms and IHS guidelines about the collection and use of research specimens can be found at: <http://www.ihs.gov/NonMedicalPrograms/Research/irb.htm>
30. The circumstances spelled out in the regulations are (1) a life threatening situation when there is no time to get consent, or (2) when consent is not feasible during specific military operations involving combat or the immediate threat of combat.
31. OHRP guidance titled "Knowledge of Local Research Context" is relevant to this issue and can be found at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm>
32. OHRP guidance to clarify this regulation can be found in decision chart 3 at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/decisioncharts.htm>
33. NBAC Report at page 72.
34. Ibid.
35. The Community Consultation was undertaken to obtain input on the responsible collection and use of samples from members of identified populations for the National Institute of General Medical Sciences Human Genetic Cell Repository. The report of the meeting can be found at <http://www.nigms.nih.gov/news/reports/communityconsultation.html>
36. NBAC Report at page 72.
37. The exception refers to instances when the proposed research is to be conducted on an American Indian or Alaska Native reservation. In that case, the tribal government has the legal authority to permit or to refuse permission for that research to be conducted.
38. International Committee of Medical Journal Editors. Protection of patients' rights to privacy. BMJ 1995; 311: 1272.
39. Foster MW, Sharp RR, Freeman WL, Chino M, Berensten D, Carter H. The role of community review in evaluating the risks of human genetic variation research. Am J Hum Genet 1999; 64 (6): 1719-1727.
40. NIH Guide for Grants and Contracts, June 5, 2000.

41. The brochure, entitled *Research on Human Specimens: Are you Conducting Research Using Human Subjects* can be found at <http://www-cdp.ims.nci.gov/policy.html>, and at the NIH site, *Bioethics Resources on the Web* at <http://www.nih.gov/sigs/bioethics/>

**APPENDIX**

**WORKING GROUP ON THE NBAC REPORT  
*RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS:  
ETHICAL ISSUES AND POLICY GUIDANCE***

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