Chapter 4
Current Guidance on the Use of Human Biological Materials in Research

In the United States, the current landscape of rules, principles, and guidelines affecting the use of human biological samples in research includes existing federal regulations, state statutes governing privacy and research use of medical records, policies developed by domestic scientific and professional societies, and guidelines developed by other countries and international organizations. When NBAC began to review the use of human biological materials in research, the work of a number of these organizations provided an understanding of the range of positions that exist among those that have carefully considered this subject. This chapter describes NBAC's interpretation of the existing federal regulations, and how the concepts of IRB review and informed consent might be viewed when considering the ethical research use of human biological materials. (Existing policies developed by scientific and professional societies and international efforts to address the topic are described in Appendix D.)

A BRIEF HISTORY OF HUMAN SUBJECTS PROTECTIONS

The modern story of human subjects protections begins with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis.[1] The Code captures many of what are now taken to be

[1] Several excellent sources trace the history of human subjects research and the development of the IRB system as a mechanism for the protection of human subjects. An account of the history of human

the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that the voluntary consent of the human subject is absolutely essential." Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw from that study at any time.[2] The Code makes no provision for waiver or omission of consent.

In the United States, federal regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status the National Institutes of Health (NIH) Policies for

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subjects research and the human subjects protection system in the United States can be found in David J. Rothman's *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (Chapters 1-5 and Epilogue) and in Dennis Maloney's *Protection of Human Research Subjects*. Rothman details the abuses to which human subjects were exposed, culminating in Henry Beecher's 1966 article, "Ethics and Clinical Research," published in the *New England Journal of Medicine*, and ultimately contributing to the impetus for the first NIH and Food and Drug Administration regulations. Other equally useful sources include Robert J. Levine's *Ethics and Regulation of Clinical Research* (Chapter 14), Joan E. Sieber's *Planning Ethically Responsible Research*, Robert M. Veatch"s "Human Experimentation Committees: Professional or Representative?," and William J. Curran's "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies."

[2] Similar recommendations were made by the World Medical Association in *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, the 35th World Medical Assembly, Venice, Italy; the 41st World Medical Assembly, Hong Kong, 1989; and the 48th General Assembly, Somerset West, Republic of South Africa, 1996. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic

the Protection of Human Subjects, which were first issued in 1966. The regulations established the Institutional Review Board (IRB) as one mechanism through which human subjects would be protected.

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and suggested guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW.

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, which set forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles—respect for persons, beneficence, and justice—are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects. The *Belmont Report* also describes how these principles apply to the conduct of research. Specifically, the principle of respect for persons underlies the need to obtain informed consent; the principle of

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research.

beneficence underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of justice requires that subjects be fairly selected.

In 1981, in response to the National Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the U.S. Food and Drug Administration (FDA) promulgated significant revisions of their human subjects regulations. The revisions did not alter the general principles of IRB review as they had evolved over the preceding three decades. Rather, they focused on the details of what the IRB is expected to accomplish and some of the procedures it must follow (Levine, 1986, p. 324).

These "basic" regulations became final January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule" as it is sometimes called) was promulgated by 16 federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted certain of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal departments and agencies. The Common Rule and other human subjects regulations are codified at Title 45 Part 46 of the Code of Federal Regulations, and it is the NIH Office for Protection from Research Risks (OPRR) that has taken the lead within the Federal Government on the task of harmonizing human subjects protections across agencies.[3]

[3] The Office for Protection from Research Risks (OPRR) fulfills responsibilities set forth in the Public

HOW DO THE REGULATIONS APPLY TO RESEARCH USING HUMAN BIOLOGICAL MATERIALS?

When applied to research using stored human biological materials, a series of initial inquiries is needed to determine whether the regulations apply at all.

1. Is the research subject to federal regulation?

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

Health Service Act. These include: (1) Developing and monitoring, as well as exercising compliance oversight relative to: (a) HHS Regulations for the protection of human subjects in research conducted or supported by any component of the Department of Health and Human Services; and (b) PHS Policy on Humane Care and Use of Laboratory Animals involved in research conducted or supported by any component of the Public Health Service; (2) coordinating appropriate HHS regulations, policies, and procedures both within HHS and in coordination with other Departments and Agencies in the Federal Government; and establishing criteria for and negotiation of Assurances of Compliance with institutions engaged in HHS-conducted or supported research involving human subjects and those engaged in PHS-conducted or supported research using animals; (3) conducting programs of clarification and guidance for both the Federal and non-Federal sectors with respect to the involvement of humans and the use of animals in research; and directing the development and implementation of educational and instructional programs and generating educational resource materials; 4) evaluating the effectiveness of HHS policies and programs for the protection of human subjects and the humane care and use of laboratory animals; and (5) serving as liaison to Presidential, Departmental, Congressional, interagency, and non-governmental Commissions and Boards established to examine ethical issues in medicine and research and exercises leadership in identifying and addressing such ethical issues.

For example, an investigator performing privately funded research at a large university that has executed a "multiple project assurance" with the Federal Government almost always will be required to abide by the federal regulations.[4] In addition, many multiple project assurance agreements include a provision that prevents researchers at that institution from evading federal regulation by conducting the research off-site or with a private, unregulated company. Instead, these multiple assurances typically promise that any researcher affiliated with the institution will abide by the federal regulations no matter where or with whom he or she works.

Thus, research on stored human biological materials carried out by a privately funded company, using only investigators who are free of affiliations with institutions that have executed a multiple project assurance, might not be subject to the federal human subjects regulations.

2. Does the activity constitute research?

The regulations do not apply to purely clinical interventions, even if they are experimental in nature. Rather, they apply to research, defined as "a systematic investigation designed to

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[4] The regulations require that each covered institution engaged in the conduct of research involving human subjects provide a written assurance of compliance, that it will comply with the requirements set forth in these regulations. The document is referred to as an "Assurance." Each Assurance sets forth the commitment of the institution to employ the basic ethical principles of the *Belmont Report* and to comply with the regulations. There are several kinds of Assurance documents. If an independent investigator is to provide an assurance of compliance to OPRR the document is called an Agreement.

develop or contribute to generalizable knowledge" (46.102(d)). If the work on the stored materials is done solely as a part of clinical intervention, as might be the case in a pathology laboratory, then the federal regulations do not apply.

Work that has both a clinical and a research component, however, is covered by the federal regulations. Thus, a pathology laboratory that saves some tissue left over from a clinical intervention in order to do further, research-oriented testing would be subject to the federal regulations.

3. Does the research involve a "human subject"?

"Human subject" is defined by the regulations as "a living individual about whom an investigator conducting research obtains: (a) data through intervention or interaction with the individual, or (b) identifiable private information" (46.102(f)(1)&(2)).

From this definition it is apparent that an investigator who interacts with a person in order to obtain a new blood or saliva sample is doing human subjects research, regardless of whether the investigator records any personal information about the subject.

When working with existing stores of biological materials, an investigator is defined as

doing research on a "human subject" when he or she obtains "identifiable private information." Section 46.102(f)(2) defines "identifiable" to mean "the identity of the subject is or may readily be ascertained by the investigator or associated with the information." OPRR interprets "identifiable" to include specimens with codes that, with the cooperation of others, could be broken open in order to reveal the name of the tissue source.[5] Thus, research on specimens provided to the investigator with no personal identifiers and where no codes linked to personal identifiers are maintained would not be covered by the regulations because no human subject would be involved.

On the other hand, research on specimens that are linked, even through a code, to personal information about the tissue source constitutes research on a human subject and is subject to the federal regulations.

For example, imagine a researcher interested in doing basic work toward the development of the mapping and sequencing of the human genome. He or she might request tissue samples from a repository that has stored samples from an entire kin group. The samples are identified by position within the kin group (e.g., "father", "daughter," "maternal aunt"), but the identity of the family was never recorded at the time the samples were collected. Thus, even if the investigator and the repository were to attempt to recontact the tissue donors, it would be impossible, because their identities are entirely unknown and unknowable. In this scenario, there would be no human

[5] Personal communication from Dr. Gary B. Ellis, Director, OPRR, April 8, 1998.

subject of research involved; no IRB review would be necessary, nor would consent from the tissue donors for new and unanticipated forms of research be required.

A murkier situation develops when tissues are identified in the HBM collection but the identifiers are stripped before release to an investigator. Imagine, for example, that an institution called HBM Collection of America ("CoA") has a number of tissues from kin groups. Investigator Smith requests samples from a kin group with achondroplasia. CoA takes samples from Family Jones, strips all references to the family name "Jones," and supplies them to the investigator marked only by position within the group, i.e., "father," "mother," "maternal aunt," "son," etc. The investigator has no way of knowing that the samples come from the Family Jones, and thinks of the samples as truly unidentifiable. If this is true, then no human subject is involved in the investigator's research on the samples, and no IRB review or informed consent is required. But if CoA has kept a record that it sent "Family Jones" -- and only Family Jones -- to the investigator, then in fact the identity of each tissue source can be nearly or completely reconstructed by combining what the investigator knows (family position) with what CoA knows (name of family). The federal regulations are ambiguous as to whether this meets the definition of "identifiable," although it would appear that it could. Keeping in mind that one of the reasons for being concerned with identifiability of the family is to assess the possibility that research information could flow back to the tissue source, this scenario appears to describe a situation in which information could be linked between the investigator and a particular member of family

(with some added difficulty if there is more than one maternal aunt or son).

Even more complex is the scenario just described, but with CoA providing samples from several kin groups, e.g. Family Jones, Family Wong, and Family Lopez. In this situation, no individual tissue source could be determined with precision, but each individual could be identified as part of the small group that makes up these three families. If the investigator were to provisionally discover that all or most of the samples provided by CoA indicated that its source was at some risk of significant illness, there could certainly be a temptation to send this ambiguous but possibly useful information back to the sources via CoA's record of which kin groups' samples were under investigation. It is unclear, again, whether samples used in this manner would constitute "identifiable" samples under the regulation, thus triggering human subjects protections. Overall, it seems unlikely, but the ambiguity in the regulatory application exists.

Finally, under the federal regulations, only living individuals can be human subjects. Research involving tissues from individuals who are deceased at the time of the research is not subject to the Common Rule, regardless of whether or not prior informed consent was obtained. Such research may, however, be subject to the requirements of applicable State law. Of course, there may be ethical concerns regarding the use of such tissues beyond the scope of current law or regulation. In addition, where research using samples from deceased individuals involves identifiable private information about their living relatives, those relatives may themselves be

human subjects" under the HHS regulations and must be afforded all required protections. Indeed, certain types of genetic research could pose risks for living relatives of the deceased. For example, if research were conducted on autopsy material of an 30-year-old woman who died in a traffic accident, and it were inadvertently found that she possessed the gene for Huntington's Disease (which might not become manifest until age 50), then that woman's children automatically move into a high-risk category for Huntington's Disease. Were they to be informed of this finding they would then face the prospects of being tested, coping with the psychosocial aspects of being at risk, and face possible future health insurance discrimination.

4. For research requiring review, what are the IRB requirements?

For situations in which individuals who provide biological material are identifiable and, therefore, the federal regulations apply, two basic protections for human subjects generally come into play. First, IRB review is required to ensure an acceptable balance between risks and benefits, and second, subject enrollment is permitted on the condition that informed consent is properly obtained. There are, however, exceptions and variations that are pertinent to research on human biological materials.

First, the twin protections of consent and IRB review do not apply if the research is found to be exempt from the federal regulations. The person given the authority to determine if an

exemption applies will vary among institutions, depending upon the assurance they negotiated with the government. In many cases, that person will be the chair of the research or clinical department in which the investigator works. In others, it will be the chair or the administrator of the IRB.

The regulations state that such an exemption may be applied to "research involving the collection or study of existing. .specimens. . .if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects" (46.101(4)).

Currently, OPRR interprets this regulation to mean that investigators who conduct research with coded samples are not eligible for the exemption if there is any means by which the codes could be broken (including by cooperation with other people and institutions) and specific research results linked to specific subjects.

On the other hand, if a coding system were developed that used encryption schemes to permit updated clinical information to flow downstream to the investigator using the specimen, but that absolutely precluded the possibility of linking a specimen upstream back to the source (including by cooperation with other people and institutions), this research would be eligible for an exemption from the requirements for subject consent and IRB review.

INFORMED CONSENT REQUIREMENTS

All human subjects research generally requires consent but this requirement can be altered or waived if certain criteria, set forth at 45 C.F.R. Sec. 46.116(d), are met:

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

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

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

4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (see flow charts for clarification).

For research with human biological materials, then, a request to waive consent by the original donor could be granted by an IRB if it could be shown that: 1) the research neither affects the rights of subject nor poses more than a minimal risk of psychosocial harm (including distress at receiving genetic information, stigmatization or discrimination if third parties become privy to the information etc); 2) it is impossible or extremely difficult to contact the tissue donors to obtain consent; and 3) a plan is made to provide information to subjects after the fact, where appropriate.

The meaning of "minimal risk," therefore, is central to determining if a protocol is eligible for a waiver of the consent requirements. One risk is that an investigator will discover something

that tempts him to communicate the results to the tissue source. This might occur, for example, when preliminary results indicate the possible presence of a dangerous condition that might be ameliorated only with immediate medical attention.

Experts disagree about whether interim or inconclusive findings should be communicated to subjects, although most agree that they should not because only confirmed, reliable findings constitute "information." Persons who oppose revealing interim findings argue that the harms that could result from revealing preliminary data whose interpretation changes when more precise or reliable data become available are serious, including anxiety or irrational (and possibly harmful) medical interventions. They argue that such harms are avoidable by controlling the flow of information to subjects and limiting communications to those that constitute reliable information. MacKay (1984), writing about the development of genetic tests, argues against revealing interim findings, contending that preliminary results do not yet constitute "information" since "until an initial finding is confirmed, there is no reliable information" to communicate to subjects, and that "even...confirmed findings may have some unforeseen limitations" [p. 3]. He argues that subjects should not be given information about their individual test results until the findings have been confirmed through the "development of a reliable, accurate, safe and valid presymptomatic test" [pp. 2-3; see also Fost and Farrell (1990)]. Others have argued that the principle of autonomy dictates that subjects have a right to know what has been learned about them, and therefore, that interim results should be shared with subjects (Veatch).

Reilly (1980) suggests that IRBs develop general policies governing the disclosure of information to subjects to help make these determinations. He suggests that at least the following three factors be considered: "1) the magnitude of the threat posed to the subject; 2) the accuracy with which the data predict that the threat will be realized; and 3) the possibility that action can be taken to avoid or ameliorate the potential injury" [p. 5]. IRBs should ask investigators to define three categories of disclosure: 1) "findings that are of such potential importance to the subject that they must be disclosed immediately;" 2) "data that are of importance to subjects..., but about which [the investigator] should exercise judgment about the decision to disclose....[i]n effect, these are data that trigger a duty to consider the question of disclosure;" and 3) "data that do not require special disclosure" [pp. 5, 12].

The Limitations of Informed Consent

A common assumption is that some version of an informed consent requirement—perhaps a very detailed and complex one—is the appropriate instrument for protecting the various interests that could be adversely affected by the practice of collecting and storing biological samples, without excessively constraining scientific research or making it too costly to pursue (Clayton, 1995).

It might be said that, independent of the functions of informed consent, a proper consideration of the individual's autonomy weighs in favor of allowing the individual maximal control over his or her sample, and that this in turn requires specific consent for particular uses of the sample.

However, it is a mistake to assume that increasing a person's range of choices will thereby enhance autonomy. In some cases, increasing the range of choices may actually diminish a person's ability to act autonomously, especially when the information needed for a responsible choice is not available (Dworkin, 19xx). Furthermore, it is also a mistake to assume that if an individual is not allowed to exercise choice over some matter his or her right to autonomy is infringed. Not every possible choice counts so far as autonomy is concerned. In general, whether the ability to make a choice represents a legitimate autonomy interest (much less an interest that deserves the protection that rights accord) will depend upon how that choice is related to the individuals other interests, to one's conception of oneself and of what is important.

Nevertheless, informed consent is now generally recognized to be both a legal and moral requirement for medical interventions generally and for all experiments on human subjects that involve more than minimal risks. Risks are taken to include not only potential physical harms from bodily invasions, but also psychosocial harms, especially stigmatization, dignatory harms, and other assaults on the individual's sense of self-worth.

Five elements of informed consent can be distinguished: 1) disclosure (of relevant risks and benefits of the procedure); 2) competence (on the part of the patient or subject) to make a decision whether to accept the treatment or participate in the research); 3) comprehension (of the relevant risks and benefits); 4) choice (an expressed decision to accept the treatment or participate in the experimentation); and 5) voluntariness (of the choice to accept treatment or to participate in research).

Clearly, informed consent will play a role in any ethically sound system for collecting and using biological samples at least to this extent: the requirement of informed consent must be met for medical treatments generally and for research (involving more than minimal risk). The question is whether an ethically sound system for collecting, storing, and using biological samples will require additional or amplified applications of the requirement of informed consent in order to reduce the risks of the various harms mentioned in chapter 3.

As already noted, the requirement of informed consent developed as a safeguard against very tangible harms, the sorts of physical harms that the law generally regards as batteries (Faden and Beauchamp, 1986). In other words, informed consent first and foremost protects individuals from nonconsensual invasions of their bodies. Informed consent was not originally invoked as a general protection against all the various harms that could result, whether directly or indirectly,

from medical interventions or from research. Even when understood as also providing protection against psychosocial harms, informed consent cannot reasonably be viewed as protecting the whole range of heterogeneous interests that may be affected by the uses of biological samples.

Moreover, even if informed consent can serve to protect against the harms of deception and manipulation, that protection might be served by disclosure of the fact that the sample will be stored and later may be used for a wide range of purposes, without requiring either general or specific informed consent. Hence it is one thing to agree that freedom from nonconsensual bodily invasions and from psychosocial harms is so important that informed consent is a necessary condition for the participation of human subjects in research, it is quite another to say that an adequate informed consent document for human biological sample practices must ensure the sample source full control over every choice that may be made in the future concerning the uses of the sample.

Two distinct but equally important points must be emphasized. First, the justification for informed consent focuses primarily on some, but not all possible harms, and not on the mistaken notion that informed consent enhances autonomy simply by virtue of multiplying choices. Informed consent is primarily a protection against nonconsensual bodily invasions and against dignatory harms that can generally be ranked under the category of treating persons disrespectfully, as if they were mere means for the pursuit of the ends of others. Informed

consent is not a device for maximizing an individual's range of choices; one would only view it in that way if one erroneously assumed that an individual's autonomy is violated whenever he is not given the widest range of choices possible.

Second, these two types of harms against which informed consent is designed to protect are certain to occur if informed consent is not secured, because nonconsensual bodily invasions and disrespectful treatment are themselves harms, quite apart from any further harms that may follow. Yet most of the harms mentioned previously are not certain to occur and in many cases are extremely unlikely to occur. It is one thing to argue that the prevention of the certain and serious harms of nonconsensual bodily invasion and disrespectful treatment justifies restrictions on research and quite another to argue that the mere possibility of various harms, some of which may not be so serious and others which are very unlikely to occur, provides an equally compelling reason to restrict research.

Furthermore, it is important to stress that the primary harm against which the requirement of informed consent is supposed to protect is a serious one: if a person is not free from unwanted invasions of this body, i.e. if their body is treated as a mere object to be dealt with as others choose, neither their life nor their liberty are secure. As reasons for restrictions on scientific research, the need to prevent nonconsensual bodily invasions and the treatment of persons as mere means, on the one hand, and the “need” to protect against a range of possible, but in some cases

highly improbable, harms of varying degrees of seriousness are not on a par. This is especially true in terms of possible harms that might occur after the sample has already been taken and hence after the risk of unwanted bodily invasion is no longer an issue. Once this fundamental point is appreciated, it becomes clear that there is a large gap between identifying various potential harms that might result from a system in which individuals lose control over what is done with their biological samples, and making a plausible case for introducing an elaborate system designed to extend their control, whether through some system of specific consent requirements or in some other way.

General Consent

One measure that has been proposed to protect against the various risks that can arise from the uses of human biological materials is a general or open-ended consent, either alone or with a requirement of specific consent for particular uses of the sample or for those types of research that might be regarded as especially problematic. Thus, for example, it has been suggested that at the time a biological sample is to be taken the potential source must be told that at that time she may consent to or object to any future research uses that may be made of the sample, so long as the sample is rendered nonidentifiable with the source, and with the additional requirement that specific permission is to be obtained from the individual for any use of the sample in which their identity could be ascertained. The chief attraction of the general consent

component of such an arrangement is that it requires in lower administrative costs than specific consent for each future use, since one informed consent process authorizes an indefinite number of future uses.

However, the difference between general consent and what is ordinarily understood by informed consent is so great that it is problematic even to use the term "consent" to refer to both. As noted earlier, a key element of informed consent is disclosure of the relevant risks and benefits of the procedure that is to be accepted or refused. The term "relevant risks" here does not mean all possible risks. In general, relevant risks are those that a reasonable person would want to be apprised of. However, for some types of decisions, a case can be made for a more "subjective" standard, i.e., a requirement that the individual must be informed of those risks that they would need to know to make a reasonable decision, given their particular values. But regardless of whether an "objective" or a "subjective" standard of relevance is employed, the rationale for informed consent presupposes the ability to identify a much more determinate and limited set of relevant risks than is generally available in the stored biological sample setting.

Thus, general consent requirements are only distantly related to informed consent and do not in this setting perform the functions of informed consent. The question remains whether general consent requirements serve any useful purpose effectively enough to warrant changing current practices to incorporate them.

EXPEDITED IRB REVIEW

For research that is not exempt from IRB review and informed consent by the subject, there are nonetheless opportunities for streamlining the review process in some cases and obviating the need for consent.

First, an IRB may use expedited review procedures when a protocol involves no more than minimal risk [46.110]. In short, the IRB chair or one or more experienced reviewers, designated by the chair from among members of the IRB, review the research and approve it or refer it to the IRB for full IRB discussion. To qualify for expedited review, an activity must: (1) involve no more than minimal risk and be found on the list published at Federal Register 46: 8392; Jan. 26, 1981;[6] or (2) be a minor change in previously approved research during the period of one year or less for which approval is authorized by the IRB.

[6] This list, which is currently being revised, includes: 1) collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth; if patient care indicates a need for extraction; 2) collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor; 3) recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practices; 4) collection of blood samples by venipuncture, in amounts not exceeding 450 ml in an 8-week period and no more often than 2 times per week, from subjects 18 years of age or older and who are in good health and not pregnant; 5) collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted techniques; 6) voice recordings made for research purposes; 7) moderate exercise by healthy volunteers; 8) the study of existing data, documents, records, pathological specimens, or diagnostic specimens; 9) research on individual or group behavior or characteristics of individuals; 10) research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required (46 FR 8392; January 26, 1981).

For research on human biological materials, a key question concerning eligibility for expedited review will be whether the research poses more than a minimal risk to the subject. This assessment will depend upon the kind of information being sought in the specimen, its psychosocial and clinical significance for the subject, and the likelihood that the finding will be transmitted to the subject, or to anyone else who could associate the findings with the subject.

Deciding whether the research represents "minimal risk" depends, in turn, on the likelihood that research information will flow back to the subject and the chance that this information will be harmful. While employment and insurance discrimination are real possibilities, a more probable source of concern is the temptation to transmit interim findings that have some tentative clinical significance.

IRB CONCERN FOR THIRD-PARTY INTERESTS

The federal regulations are focused on individuals. They ask if an individual is "identifiable." If they are, this individual is almost always entitled to be asked whether they wish to be a human subject of research. The IRB is asked to review the protocol to assess its risks and benefits to each individual subject. Nowhere in this process are the concerns of third parties explicitly taken into account.

And yet, research on one individual may reveal important, even dangerous information

about others. Genetic testing on corpses, as noted above, can yield information on living relatives. And testing on a number of disparate individuals may yield information pertinent to many unrelated people who share salient characteristics, such as race, ethnicity, or the presence of a predisposing condition. This, in turn, could result in members of the group facing, among other things, stigmatization and discrimination in insurance and employment. What is at issue for both the individual research subject and the group is that the research might expose facts about them -- namely, the higher probability of the occurrence of disease -- which places them at risk of psychosocial harms.

Interestingly, there may even be circumstances where the individual research subject faces less risk of harm than other members of a group to which he or she belongs. For example, a socially and economically well-situated research subject will likely be a lower risk of suffering the effects of insurance and employment discrimination than less fortunate members of the group. Moreover, the stigma associated with a disease may be far more injurious to a group and its members than to a particular individual, especially where the group is one that is already socially and politically marginalized.

The strict focus that the regulations place on the interests of the individual research subject can be problematic in the context of research with human biological materials, and some attention should be paid to considering ways in which third party interests can be protected.

(Recommendations in this area appear in chapter 5.)

APPLYING THE REGULATIONS TO A TYPICAL PROTOCOL: ISSUES FOR IRBS

Imagine a hypothetical gene for a form of prostate cancer. Researchers might wish to screen large numbers of samples of prostate tissue currently stored in academic and commercial repositories, in order to identify those with markers for the gene. Having identified this subset, investigators might then wish to examine the medical records of those men who appear to have the gene, to correlate such things as medical history, symptomology, characteristics of the tumor, treatment choices, and outcomes. This work, in turn, might result in further subsets worthy for a more refined study, to correlate the gene with a particular type of tumor or response to treatment.

Under current regulations, any link between the specimens used by the researcher and the men from whom the materials were obtained would make the activity "human subjects research." This identifiability, even if mediated by coding systems, would trigger the requirement for IRB review. Absent encryption schemes that allow only unidirectional flow of information, IRB review could not be waived. The review might be eligible for expedited procedures, however, if it were deemed to be of minimal risk to the subjects and is eligible for expedited review (See Tables x and y).

The initial screen of all samples, done solely for the purpose of identifying which men have the gene, might qualify as minimal risk, depending on the likelihood that any finding would be communicated to the individual tissue donors and whether such communications pose the risk of significant psychosocial distress.

On the second screen, in which the subset of men whose tissues show a marker for the gene will have their medical records examined, the same issues about minimal risk apply, but with a seemingly greater risk that findings will develop in the course of research that might prompt investigators to consider communicating their finding to the tissue donors or their physicians. For example, if the data strongly indicate that those with the markers respond dramatically better to one treatment than another, investigators may wonder whether it would be best to communicate this information to patients and their physicians so that the better treatment can be pursued before the patient's health irreversibly declines.

At the same time, the tentative nature of these findings may make their communication problematic. Since some prostate treatments may have significant side-effects, such as impotence and incontinence, and since the clinical data on the need to detect and treat slow-growing prostate cancers in older men is mixed, such tentative findings may put patients into a position of great uncertainty and anxiety, without the assurance of clinical benefit.

It is the difficulty of understanding the meaning of "minimal risk" with regard to psychosocial harm (as opposed to physical harm) that makes this issue so complex, and, in turn, makes the decision about eligibility for expedited review so difficult.

Psychological risk includes the risk of harm from learning genetic information about oneself (e.g., that one is affected by a genetic disorder that has not yet manifested itself). Complicating the issue of communicating genetic information to a subject is that often the information is limited to probabilities. Furthermore, the development of genetic data carries with it a margin of error; and some information communicated to subjects will, in the end, prove to be wrong. In either event, participants are subjected to the stress of receiving such information. For example, researchers involved in developing presymptomatic tests for Huntington Disease have been concerned that the emotional impact of learning the results may lead some subjects to attempt suicide. They have therefore asked whether prospective participants should be screened for emotional stability prior to acceptance into a research protocol.

Note that these disclosures of information can also be beneficial to the subject. One of the primary benefits of participation in genetic research is that the receipt of genetic information, however imperfect, can reduce uncertainty about whether participants will likely develop a disease that runs in their family (and possibly whether they have passed the gene along to their children). Where subjects learn that they will likely develop or pass along the disease, they might plan

differently for the future. To minimize the psychological harms presented by pedigree research, it would be prudent for IRBs to make sure that investigators will provide for adequate counseling to subjects on the meaning of any genetic information they might receive. Genetic counseling is not a simple matter and must be done by persons qualified and experienced in communicating the meaning of genetic information to persons participating in genetic research or persons who seek genetic testing.

As noted in chapter 3, social risks include stigmatization, discrimination, labeling, and potential loss of or difficulty in obtaining employment or insurance.[7] Changes in familial relationships are also among the possible social ramifications of genetic research.

Regardless of whether expedited review is permitted by the local IRB or standard review is required, the IRB may then consider whether subject consent to do the research can be waived. Once again, the question of minimal risk must be answered. In addition, the investigators would need to show that doing the research without subject consent is necessary because it is impractical

[7] For example, an employer who knew that an employee had an 80 percent chance of developing HD in her 40s might deny her promotion opportunities on the calculation that their investment in training would be better spent on someone without this known likelihood. Of course, the company may be acting irrationally (the other candidate might be hit by a car the next day, or have some totally unknown predisposition to debilitating disease), but the risk for our subject of developing HD is real, nonetheless. One problem with allowing third-parties access to genetic information is the likelihood that information, poorly understood, will be misused. Likewise, an insurer with access to genetic information may be likely to deny coverage to applicants when risk of disease is in an unfavorable balance. Insuring against uncertain risks is what insurance companies do; when the likelihood of disease becomes more certain, they may refuse to accept the applicant's "bet."

to contact the donors, and that doing the research without consent will not affect the rights of the subjects.

Given the subtlety of these inquiries, it would not be surprising to find that IRBs have different rulings. Some, for example, might find that the initial screening to identify the subset of samples with markers for the gene ought to be eligible for expedited review and a waiver of consent, but that subsequent work on the subset ought to require full review and subject consent. Others might waive consent for all aspects of the research, and still others for none.

This variability in IRB response is relevant, because many protocols will involve repositories at one institution, and investigators at one or more different institutions. Since the regulations require that each institution's own IRB conduct its own review, the repository and the investigators may find that they are being held to different rules about the need to obtain consent. This phenomenon, a common occurrence in collaborative research of all types, has drawn criticism from the research community, as it adds to the time and complexity of getting all necessary approvals. For example, a researcher at Institution A, which has decided that consent is required for all stages of the work, might be precluded from collaborating with an investigator from Institution B, where consent requirements were waived. The decision about whether to permit the collaboration will lie in the hands of Institution A's IRB.

The justification for multiple IRB reviews lies in part in the philosophy of local review to reflect local standards of human subjects protections, and in part on the expectation that IRBs are fallible, and that multiple reviews minimizes the possibility of a serious error due to the incorrect ruling by one particular IRB.

OTHER CONSIDERATIONS: MEDICAL RECORD PROTECTION AND HUMAN SUBJECTS RESEARCH

Many of the protocols calling for research use of human biological materials will also require that information be obtained from relevant medical records to supplement the tissue. This will allow investigators to correlate characteristics of the tissue with characteristics of the etiology and course of the patient's disease and the patient's response to various treatments. Thus, it is not enough to look only at the rules currently governing access to human tissue for research; one must also look at rules governing access to medical records. Where changes are contemplated in the current regime governing tissue research, it will be important to ensure that the changes are compatible with rules governing medical records that will be used in conjunction with that research.

The federal regulations that govern human subjects research have provisions that apply to the use of medical records. Efforts to link one record with another, or to link a record with an interview of the patient, are considered "research" under the federal definitions. If the records

have any personal identifiers, then this constitutes human subjects research, and requires IRB review and patient/subject consent, subject to the same exceptions outlined above for research on the patient/subject's tissue. Indeed, the regulations governing tissue use and record use are basically the same, and on a practical level treat tissue as simply another form of a medical record.

As noted above, however, many investigators work in settings not covered by the federal regulations. In these settings, few explicit limitations against in state or federal law on their use of medical records for research.[8] There are more general rules, both statutory and common law, however, that do lay the groundwork for a claim of privacy as against nonconsensual use of medical records.

Nearly every state has laws or regulations that provide varying degrees of protection for information contained within medical records.[9] The Privacy Commission, however, noted that "the typical statutory prohibition against the disclosure of medical-record information by medical professionals is focused on protecting the professional, not the patient." [10]

More recently, though, states have adopted these statutes to protect the citizen rather than the professional, albeit most often in the context of protecting records about only certain diseases

8 William H. Minor, "Identity Cards and Databases in Health Care: The Need for Federal Privacy Protections," 28 Colum. J.L. & Soc. Probs. 253 (Winter 1995).
9 Robert E. Smith, Compilation of State and Federal Privacy Laws (1992)
10 Privacy Protection Study Commission, Personal Privacy in an Information Society (1977).

or, most often HIV, AIDS, and various mental illnesses.[11] The variability of state law protection has been cited as a problem in itself, regardless of the protections offered by the states. [12]

Where state statutes exist, they may specifically contemplate access to medical records for research use. California's medical records confidentiality law, for example, states that the "information may be disclosed to public agencies, clinical investigators, health care research organizations, and accredited public or private nonprofit educational or health care institutions for bona fide research purposes. However, no information so disclosed shall be further disclosed by the recipient in any way which would permit identification of the patient." [13] It is interesting to note, though, that the California law has a section outlining special penalties for unauthorized, identifying releases of genetic information.

No federal law protects the privacy of medical records, unless the records are actually held by the government, and it has been noted that the areas to which Congress has chosen to extend privacy protection -- including credit protection,[14] electronic communications[15], and video rental lists[16] -- provide a dramatic contrast to the lack of a federal law covering the confidentiality of

11 See Compilation of Privacy Laws; Office of Technology Assessment, U.S. Congress, Protecting Privacy in Computerized Medical Information(1993); Sheri Alpert, "Smart Cards, Smarter Policy: Medical Records, Privacy, and Health Care Reform," 23 Hastings Center Rep., Nov.-Dec. 1993.
12 Marianne Lavelle, Health Plan Debate Turning to Privacy, Nat'l L.J., May 30, 1994, at A1.
13 Cal. Civ. Code Sec. 56.10 (c)(7).
14 See Fair Credit Reporting Act of 1970, Pub. L. No. 91-508, 84 Stat. 1114 (codified as amended at 15 U.S.C. section 1681 (1988)).
15 See Omnibus Crime Control and Safe Streets Act of 1968, tit. III, the Electronic Communications Privacy Act of 1968, Pub. L. No. 90-351, section 802, 82 Stat. 212 (codified as amended at 18 U.S.C. sections 2510-2521 (1988)).
16 See Video Privacy Protection Act of 1988, Pub. L. No. 99-508, 100 Stat. 1860 (codified at 18 U.S.C. section 2701

privately-held medical records.

Courts have only recently recognized an explicit individual privacy right with respect to one's medical records. Early cases viewed unauthorized disclosure as a form of breach of statutory duty, libel, malpractice, breach of trust, and breach of contract. The language in one New York case, however, is quite strong in its condemnation of what it deemed a tortuous claim for unauthorized revelation of medical secrets: "Despite the fact that in no New York case has such a wrong been remedied due, most likely, to the fact that so few physicians violate this fundamental obligation, it is time that the obligation not only be recognized but that the right of redress be recognized as well." [17] Similarly, a Third Circuit federal appeals court recognized a privacy right against a request by the government for access in order to investigate alleged health hazards.[18] The court then balanced this right against seven factors: "the type of record requested, the information it does or might contain, the potential for harm in any subsequent nonconsensual disclosure, the injury from disclosure to the relationship in which the record was generated, the adequacy of safeguards to prevent unauthorized disclosure, the degree of need for access, and whether there is an express statutory mandate, articulated public policy, or other recognizable public interest militating toward access." In that particular case, the court held that "the public need prevailed over the claim that medical records in general were protected from discovery." If such an analysis were done to balance assertions of a privacy right against the needs of

(1988).
17 93 Misc. 2d 201 (N.Y. Sup. Ct. 1977).
18 United States v. Westinghouse Electric Corp., 638 F.2d 570 (3d Cir. 1980).

investigators for nonconsensual access to medical records, it is not clear that access would be granted for all protocols.

More recently, the Second Circuit found that an individual has a constitutional right to privacy in his HIV status "because his personal medical condition is a matter that he is normally entitled to keep private."[19] Again, it is unclear how this would apply in a medical research setting, but it is significant for its explicit reliance on constitutional levels of protection for one's right to keep medical information private. In some jurisdictions, state constitutional provisions offer privacy protection [20]

CONCLUSIONS

In most cases it appears that the existing federal regulations governing research with human subjects adequately protect individuals whose biological materials are used in research. However, there are some notable ambiguities. First, the current regulations do not make completely clear what is meant by "identifiability" when determining whether in fact a human subject is involved in research on biological samples. Thus, there is resulting confusion about

19 Doe v. City of New York, 15 F.3d 264 (2d Circuit, 19--).

20 See, e.g., Alaska Const. art. I, section 22; Ariz. Const. art. II, section 8; Cal. Const. art. 1, section 1; Fla. Const. art. I, sections 12, 23; Haw. Const. art. 1, section 6; Ill. Const. art. I, section 6; La. Const. art. I, section 5; Mont. Const. art. II, section 10; N.Y. Const. art. I, section 12; S.C. Const. art. I, section 10; Wash. Const. art. I, section]. Generally, they require that state action must have caused the violation for protections to apply[7.See, e.g., Me. Rev. Stat. Ann. tit. 17-A, section 511 (West 1983); Mass. Gen. Laws Ann. ch. 214, section 1B (West 1986); Neb. Rev. Stat. section 20-201 to -211 (1991); R.I. Gen. Laws section 9-1-28.1 (1985); Utah Code Ann. section 76-9-401 (1990); Wis. Stat. Ann. section 895.50 (West 1983).]. California's constitutional privacy right is more explicit; it can be applied to privacy infringements by private parties. [Cal. Const. art. 1, section 1.]

whether certain research is covered (based on how closely the samples are linked to their sources and how easily that linkage can be accomplished). The issue of identifiability is further confounded by the researcher's growing ability to identify the source (even when unidentified) because of the uniqueness of the clinical information that accompanies the material when it is delivered from the repository.

Second, the existing regulations are silent on the topic of group or community harm. Thus, protocols that pose insignificant risks to individuals but might implicate strong group interests do not get special IRB attention. This has implications for groups such as kindreds or ethnic and racial subpopulations as well as collectivities of individuals who share a common trait, such as a genetic condition or disease status.

Third, the regulations offer insufficient guidance on the meaning of "minimal" psychosocial risk or the nature of the subjects' "rights and welfare" to be protected.

Fourth, the existing regulations do not make clear the status of living relatives of deceased individuals whose stored samples are used in research. Although OPRR has indicated that these people might in fact be considered human subjects by virtue of their genetic relationship to the sample source, the regulations do not specify how this consideration is to be handled by IRBs.

Despite the fact that the current regulations apply in most cases, other issues pertaining to adequate protections arise. For example, provision of informed consent is a required but insufficient protection of both the interests of the research subject and the investigator. Moreover, there might be overriding state laws that apply regarding the research use of medical records, thereby limiting the ability of researchers to gather unlimited information from individuals whose names are linked to the biological material.

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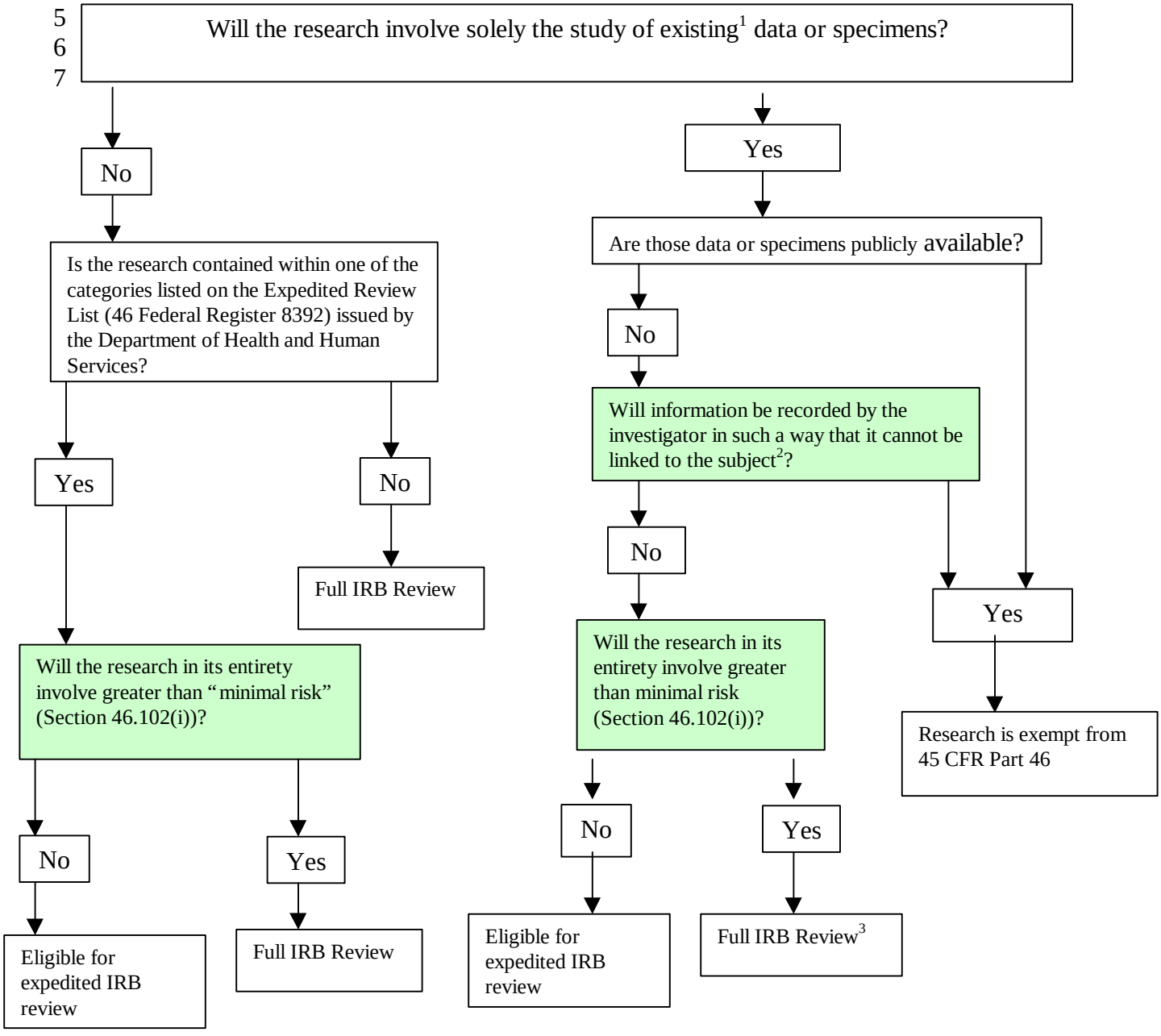
Table x: **IRB Review for Research with Human Biological Materials**

Guidelines for applying the exemption stated at 45 CFR 46.101(b)(4)



Question which may benefit from interpretive guidance.

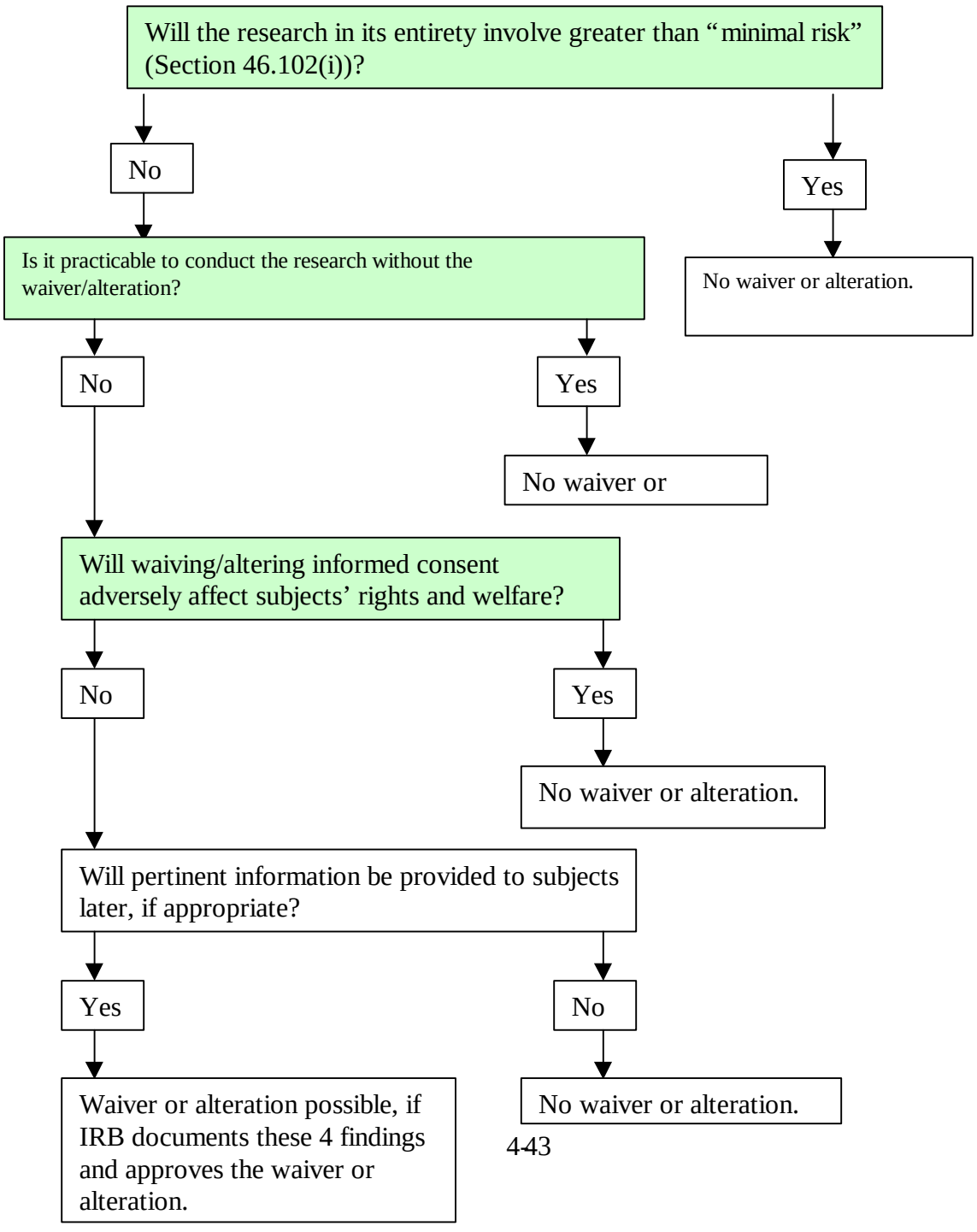
[1] "Existing" means collected (i.e., on the shelf) prior to the research for a purpose other than the proposed research. It includes data or specimens collected in research and nonresearch activities.

[2] This question is relevant to determine both (1) Is the definition of "human subject" at Section 46.102 (f) met in this research activity?, and (2) Is the research exempt in accordance with Section 46.101 (b)(4)?

[3] Research is also eligible for expedited IRB review if the subject of review involves exclusively minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Table y: **Informed Consent Requirements for Research with Human Biological Materials**

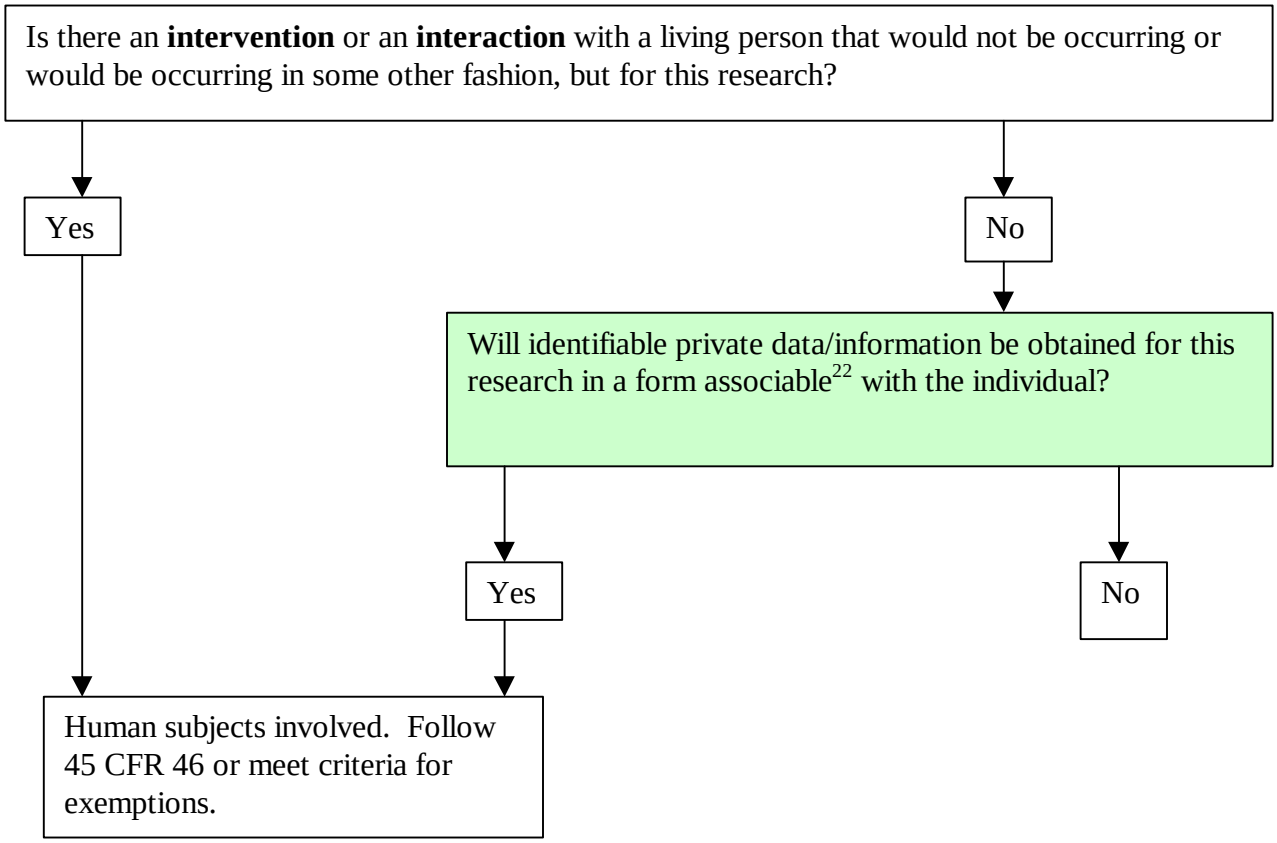
Can the Institutional Review Board employ §46.116(d) to waive informed consent or alter informed consent elements?



Questions which may benefit from interpretive guidance.

Table z: **Human Subject, Defined**[21]

Is the definition of "human subject" at Section 46.102 (f) met in this research activity?



21 Office for Protection from Research Risks, April, 1996.

22 That is, the identity of the subject is or may readily be ascertained or associated with the information.