Touro College School of Health Science

Institutional Review Board Guidebook

Edited February 1, 2008

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JURISDICTION OF THE INSTITUTIONAL REVIEW BOARD

Touro College, School of Health Science (SHS) Institutional Review Board (IRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the college. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and college policy. Research approved by an IRB is subject to review and disapproval by officials of the college. However, those officials may not approve research that is disapproved by the IRB.

The IRB functions independently of, but in coordination with other committees. For example, SHS has different professional educational departments (physical therapy, nursing etc.) which review protocols to determine whether the program should or should not support the proposed research. The IRB, however, makes its independent determination whether to approve or disapprove the protocol based upon whether or not human subjects will be adequately protected.

Whenever the SHS IRB reviews a protocol, relies on the question of whether or not the IRB has jurisdiction over approval of the research. That is, the IRB must ask, "Is the research subject to IRB review?" The federal regulations apply "to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency" that has adopted the human subjects' regulations. For example, tissue or animal studies are not reviewable by this committee.

The first two questions the IRB faces are whether the activity involves *research*, and second, whether it involves *human subjects*. **Research** is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge". **Human subjects** are defined by the regulations as "living individual(s) 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". It also goes on to define the meanings of such terms as "intervention" and "private information."

In addition, some research that involves human subjects may be exempt from the regulations requiring IRB review. Examples include educational testing and survey procedures where no identifying information will be recorded that can link subjects to the data. Disclosure of the data will not take place so that subjects will not be at risk of any civil or criminal liability. This includes any information that may be damaging to the subjects' financial standing, employability, or reputation as well as any research that involves the use of existing data, documents, or specimens, where no identifying information will be recorded that can link subjects to the data.

EXEMPTIONS TO IRB PROCEDURES

The following are specific rules for those exemptions as voted by the committee on February 1, 2008 under Exempt Research 45 CFR 46.101(b) for a flowchart go to Charts (1-11) at the end of this document. The decision whether research meets this criteria will be made by the department chairperson or someone assigned by them. The chairperson will be required to submit the exemption in writing to the committee.

Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, **unless:** (i) the information obtained is recorded in such a manner that subjects can be identified, directly or through identifiers linked to the subjects; and (ii) disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b) (2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or 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.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine; (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level found to be safe, or agricultural chemical or environmental contaminants at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

EXPEDITED REVIEW

Expedited Review requiring only review of two members of the committee will be allow under the following circumstances as voted by the committee on February 1, 2008 based upon 45 CFR 46.110 and 21 CFR 56.110. The SHS IRB chairperson or the vice chairperson (who will be nominated and elected at the SHS IRB meeting) will make the decision as to whether the IRB meets these criteria. If a study does not meet the requirements of an expedited review, all members of the committee will review it.

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or may be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review expedited or convened by the IRB.

(F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

RESEARCH CATEGORIES

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subjects privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural

beliefs or practices, and social behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Rule if either member of expedited review rejects proposal on safety issues

As voted on in full meeting of the IRB committee on February 1, 2008. If any reviewer cannot be satisfied with safety of the experiment, the researcher will be given the option of meeting with the committee with a two-week notice of the full committee. A quorum for these meetings will be five members; a super majority vote of seventy five percent will be required to approve a research project. Discussion and vote will take place in absence of anyone connected to the project including the individual making the presentation.

B. ADMINISTRATION

MEMBERSHIP

Federal Policy Requirements.

SHS IRB has an IRB with a minimum of eight members at least two of whom are not employed by or otherwise affiliated with Touro College. The SHS IRB will maintain individuals from at least three allied health science professions to review research applications.

The SHS IRB will make every effort to be nondiscriminatory to ensure that it does not consist entirely of men or entirely of women. Selections will not, however, be made based on gender. The SHS IRB will at its discretion, invite individuals with competence in special areas to assist in the review of issues, which require expertise beyond or in addition to those that are available on the IRB. These individuals may not vote.

No SHS IRB member may participate in the review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

A list of current IRB members will be submitted to OPRR and will be kept with the IRB's records. The list will identify members by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the College (*e.g.*, full-time employee, stockholder, unpaid consultant, or board member). Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of a DHHS-approved Assurance. In the latter case, changes in memberships are to be reported to OPRR.

IRB CONSIDERATIONS

An SHS IRB can have as many members as necessary for it to perform its duties effectively. Care will be taken, however, to ensure that it does not become so large that its management becomes cumbersome.

The nonaffiliated member of the IRB will be drawn from the local community-at-large. Ministers, teachers, attorneys, business persons, or homemakers are possible candidates. The person selected should be knowledgeable about the local community and be willing to discuss issues and research from that perspective. Consideration will be given to the type of community from which the institution will draw its research subjects. It is understood that nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

An investigator can be a member of the SHS IRB, however, there is a stipulation that must be adhered to without exception: The investigator-as-member cannot participate in the review and approval process for any project in which he or she has a present or potential conflict of interest. Where the investigator-member has a conflicting interest, he or she should be present only to provide information requested by the IRB. He or she should be absent from the meeting room during the discussion and voting phases of the review and approval process. SHS IRB minutes should reflect whether these requirements have been met. In addition, chairpersons of departments of research being done in their departments, except when reviewing to see if they meet the exemptions to IRB review, (Exempt Research 45 CFR 46.101(b)), will not conduct review.

The SHS IRB chairperson will be chosen by the Dean of the School of Health Science. It is expected that any person chosen will and must be perceived to be fair and impartial, immune from pressure either by the college's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources.

RECORD KEEPING

SHS IRB, will maintain both hard and soft copies of the IRB material at voted by the committee on February 1, 2008. Information on all projects will be available to all committee members on a coded site on the internet. Secondly, a locked room with a locked filed cabinet will kept. These files will contain copies of all research proposals reviewed, minutes of SHS IRB meetings, records of continuing review activities, copies of all correspondence between the SHS IRB and investigators, and statements of significant new findings provided to subjects.

Minutes of SHS IRB meetings will be kept in sufficient detail to record the following information: attendance at each meeting; actions taken by the IRB; the vote on actions taken (including the number of members voting for, against, and abstaining); the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their outcomes.

SHS IRB records must be retained for at least three years. Records pertaining to research that is conducted must be retained for three years after completion of the research. All records will be accessible for inspection and copying by authorized representatives of the department or agency supporting or conducting the research at reasonable times and in a reasonable manner.

RESPONSIBILITIES

Touro College will comply with the requirements of the Federal Assurance Policy along with any research that has been reviewed and approved by an IRB established in accordance with the requirements of the Federal Policy.

Of course, research conducted poorly as to invalidate the research, or that which exposes subjects and the college to unnecessary risk will be avoided. Approval procedures of the committee have been devised so that the college supports only well-designed and properly executed research.

THE ASSURANCE

As a college involved in both biomedical and behavioral research, we have in place a set of principles and guidelines that govern the institution, its faculty, and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution. Regardless of the source of funding, Touro College SHS IRB will follow the guidelines of The *Belmont Report.* (Appendix 1).

COMMUNICATION

Touro College assures that open channels of communication are maintained at all levels. It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of a research project directly to the appropriate institutional officials. It is vital that SHS IRB members, department heads, and other officials with responsibility for oversight of research, have open and ready access to the highest levels of authority within the institution.

PROCEDURES AND GUIDELINES

Touro College has prepared written procedures and guidelines to be followed by the SHS IRB when conducting its initial and continuing review of research, and for reporting its findings and actions to the investigator and the administration of the institution. No project will be approved for more than one year and any untoward results must be reported to the committee as quickly as reasonably possible to the chairperson or in his absence to the assigned vice chairperson by phone or mail depending upon the urgency. Any changes in procedures must be reported to the committee for reevaluation. Changes in SHS IRB approval that has already been given may not be initiated without additional IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects.

THE AUTHORIZED INSTITUTIONAL OFFICIAL.

The designated institutional official is the Dean of the School of Health Sciences assigned by the President of Touro College.

OTHER INSTITUTIONAL PERSONNEL.

IRB committee will train all new personnel about applicable procedures. Personnel involved in the conduct of research should receive additional training in institutional expectations and specific regulations pertaining to research. Training designed to enhance the development of high quality proposals should be encouraged. IRB members and others charged with responsibility for reviewing and approving research should receive detailed training in the regulations, guidelines, and policies applicable to human subject's research. Attending workshops and other educational opportunities focused on SHS IRB functions will be encouraged and supported to the greatest extent possible. Training in good research practices and in methods for minimizing risk shall be provided at the program level. In addition, IRB members will be available for consultation. Since research conducted by others may have a bearing on research projects conducted by or at the institution, journals and other research-related materials will be available to staff. All SHS IRB members shall be require submitting proof of completion of the IRB training program given by the National Cancer Society, http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp Within six months of membership, proof of completion of training program is required to be submitted to the IRB department.

INTERNAL AUDITS.

Touro College will make internal audit procedures to assure the institution's administration that its policies and procedures will be adhered to.

C. PRINCIPAL INVESTIGATORS

IRB CONSIDERATIONS

The qualifications of the principal investigator will be considered when reviewing proposals. The investigator's professional development should be taken into account and related to the degree of the protocols complexity and risk to human subjects. IRBs may require less experienced research investigators to be sponsored by seasoned researchers. Proposals that require skills beyond those held by the principal investigator should be modified to meet the investigator's skills, have additional qualified personnel added, or be disapproved.

Research investigators shall prepare protocols giving complete descriptions of the proposed research. The research plan must include provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed. Samples of informed consent documents must be included with protocols, **including a way to contact the SHS IRB committee by mail and phone.** Research investigators are responsible for obtaining informed consent and ensuring that no human subject will be involved in the research prior to obtaining the consent.

The research plan must address quality assurance standards set by the institution. In addition, applicable external standards for quality assurance must be met. External standards are of particular concern for research conducted in clinical facilities. Appropriate reviews for scientific merit must be conducted before the research is approved. Mechanisms for monitoring the progress of the research must be in place.

Research investigators, through their research design, determine whether the proposed research will involve human subjects. When it is not clear whether the research will involve human subjects, investigators should seek assistance from the SHS IRB in making this determination

Researchers are responsible for complying with all SHS IRB decisions, conditions, and requirements. Research investigators are responsible for reporting the progress of the research to the IRB and/or appropriate institutional officials as often as, and in the manner prescribed by the IRB, no less than once per year.

D. COMPLIANCE / NONCOMPLIANCE

INTRODUCTION

Touro College has attained Assurance Certification and will strive to maintain it by following appropriate regulations.

IRB CONSIDERATIONS

METHODS FOR ENSURING COMPLIANCE

To ensure compliance with the regulations, Touro College has adopted internal self-assessment procedures and practices designed to assure proper protocol and consent document preparation, protocol submission, review and approval by the IRB, and timely monitoring of protocol implementation. Touro College SHS IRB will require expiration date stamps on consent documents and protocols to ensure that the federal requirement of at least annual SHS IRB reviews of each protocol is met.

INVESTIGATING ALLEGED NONCOMPLIANCE

The SHS IRB committee will conduct itself in full awareness that under HHS regulations at 45 CFR 5, documents related to compliance oversight evaluations may be subject to the provisions of the Freedom of Information Act (FOIA).

Materials will be maintained so that under HHS regulations at 45 CFR 5b, records, which can be retrieved by an individual's name or other personal identifier, are subject to the provisions of the Federal Privacy Act.

NONCOMPLIANCE BY INVESTIGATORS, IRBS, AND INSTITUTIONS

Investigators:

Regardless of investigator intent, unapproved research involving human subjects places those subjects at an unacceptable risk. When unapproved research is discovered, the SHS IRB and Touro College, will act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the investigator's fitness to conduct human subject research. Beyond the obvious need to protect the rights and welfare of research subjects, the credibility of the SHS IRB is clearly at stake. In addition, any serious or continuing noncompliance with DHHS human subjects' regulations or the determinations of the IRB, will be promptly reported to the OPRR office.

APPENDIX 1

THE BELMONT REPORT

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called ”experimental” when the terms ”experimental” and ”research” are not carefully defined.

For the most part, the term”practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term”research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is ”experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

PART B: BASIC ETHICAL PRINCIPLES

B. Basic Ethical Principles

The expression “basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, those individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities, which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients ”according to their best judgment.” Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer-term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research-involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. However, the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment purposes. It is

necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property based on which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently, these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project; long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

PART C: APPLICATIONS

C. APPLICATIONS

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension

The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. In addition, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. However, undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified based on a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often

ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation).

(iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. SELECTION OF SUBJECTS.

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus, injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being

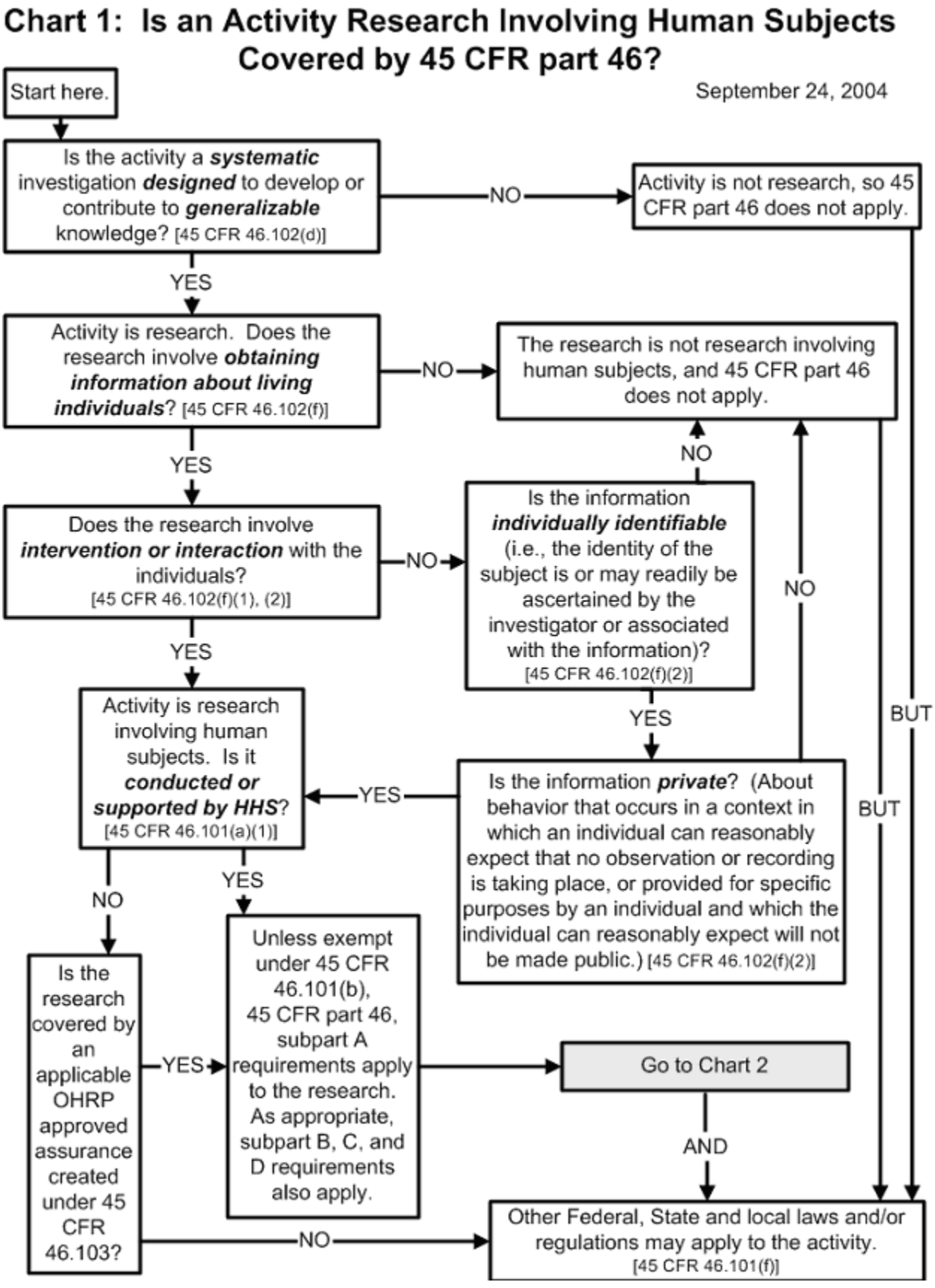
involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

(1) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

(2) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

(3) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

Charts 1-11 Charts to Determine Exemptions to IRB process.



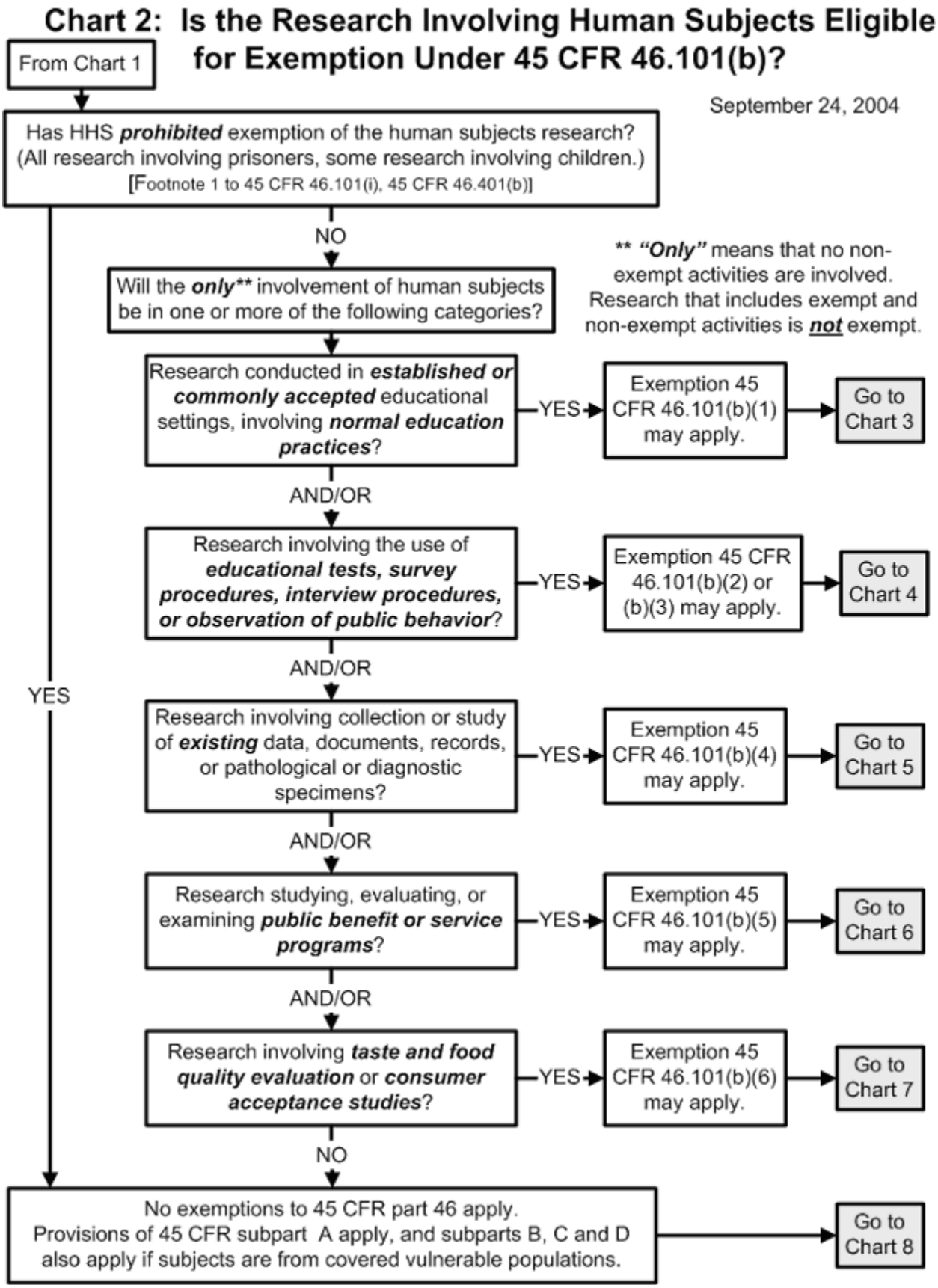


Chart 2: Is the Research Involving Human Subjects Eligible for Exemption Under 45 CFR 46.101(b)?
From Chart 1
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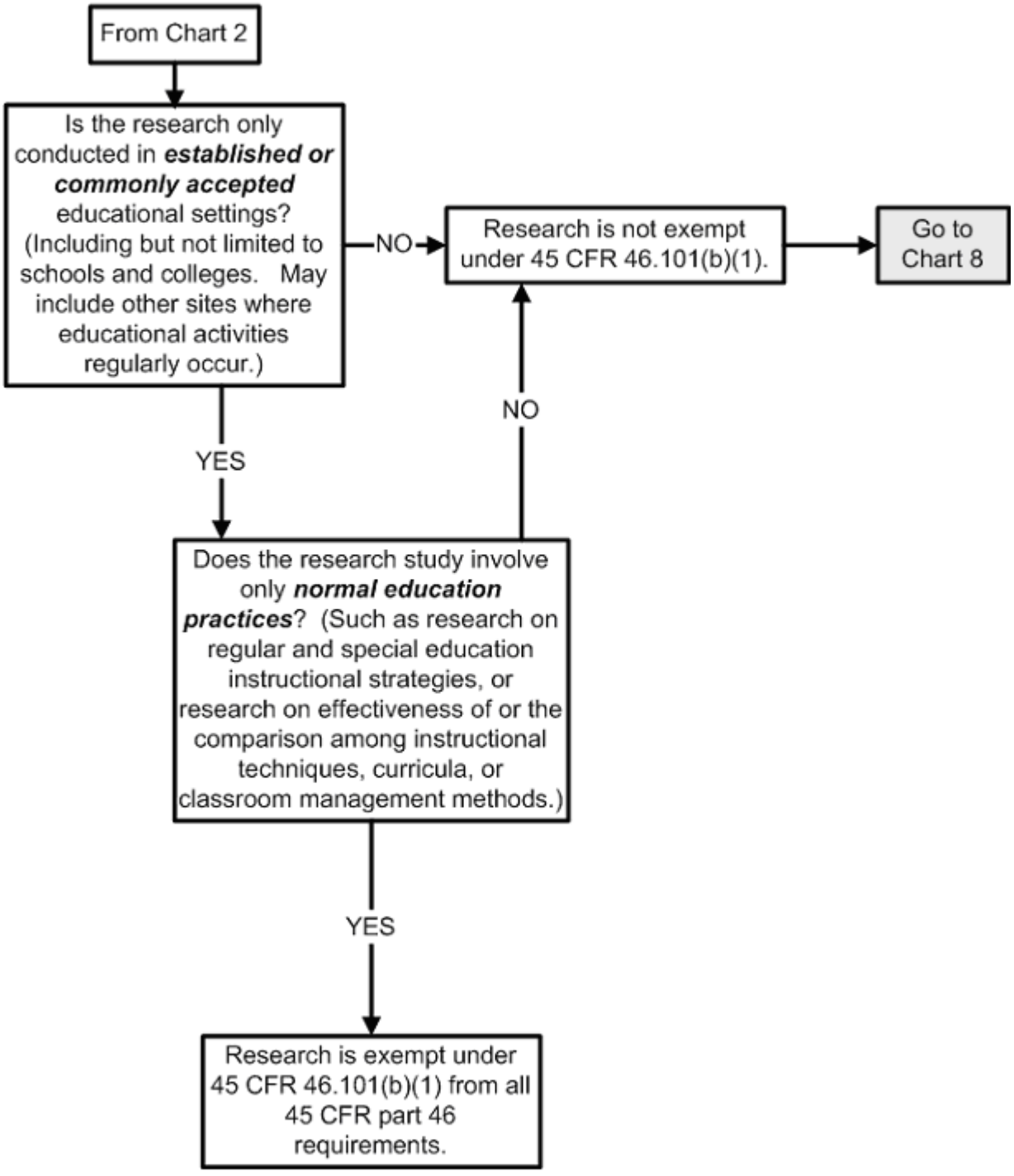
Has HHS prohibited exemption of the human subjects research? (All research involving prisoners, some research involving children.) [Footnote 1 to 45 CFR 46.101(i), 45 CFR 46.401(b)]
NO
YES
** "Only" means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is not exempt.
Will the only** involvement of human subjects be in one or more of the following categories?
Research conducted in established or commonly accepted educational settings, involving normal education practices?
YES
Exemption 45 CFR 46.101(b)(1) may apply.
Go to Chart 3
AND/OR
Research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior?
YES
Exemption 45 CFR 46.101(b)(2) or (b)(3) may apply.
Go to Chart 4
AND/OR
Research involving collection or study of existing data, documents, records, or pathological or diagnostic specimens?
YES
Exemption 45 CFR 46.101(b)(4) may apply.
Go to Chart 5
AND/OR
Research studying, evaluating, or examining public benefit or service programs?
YES
Exemption 45 CFR 46.101(b)(5) may apply.
Go to Chart 6
AND/OR
Research involving taste and food quality evaluation or consumer acceptance studies?
YES
Exemption 45 CFR 46.101(b)(6) may apply.
Go to Chart 7
NO
No exemptions to 45 CFR part 46 apply.
Provisions of 45 CFR subpart A apply, and subparts B, C and D also apply if subjects are from covered vulnerable populations.
Go to Chart 8

Chart 3: Does Exemption 45 CFR 46.101(b)(1) (for Educational Settings) Apply?



September 24, 2004

Chart 4: Does Exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?

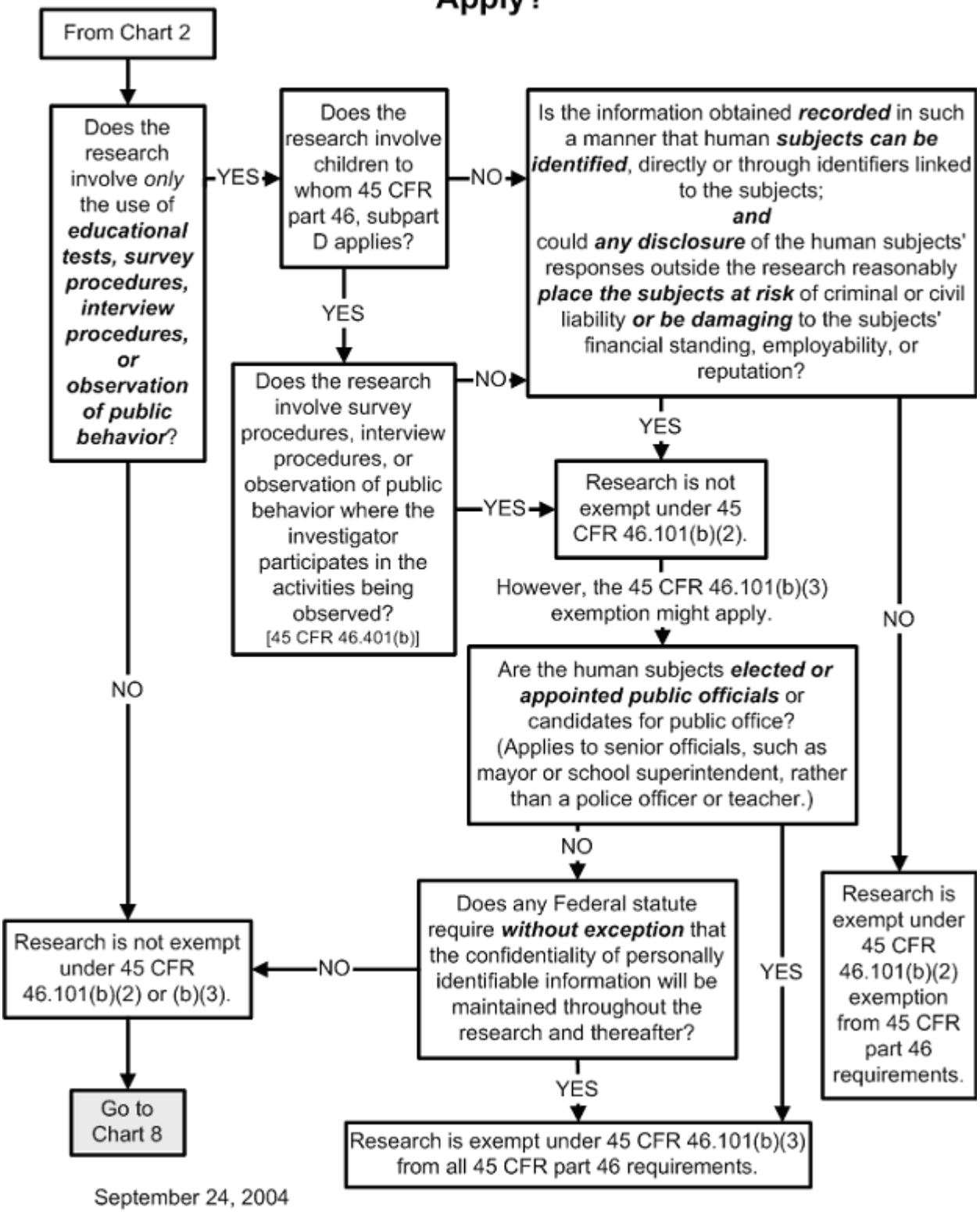


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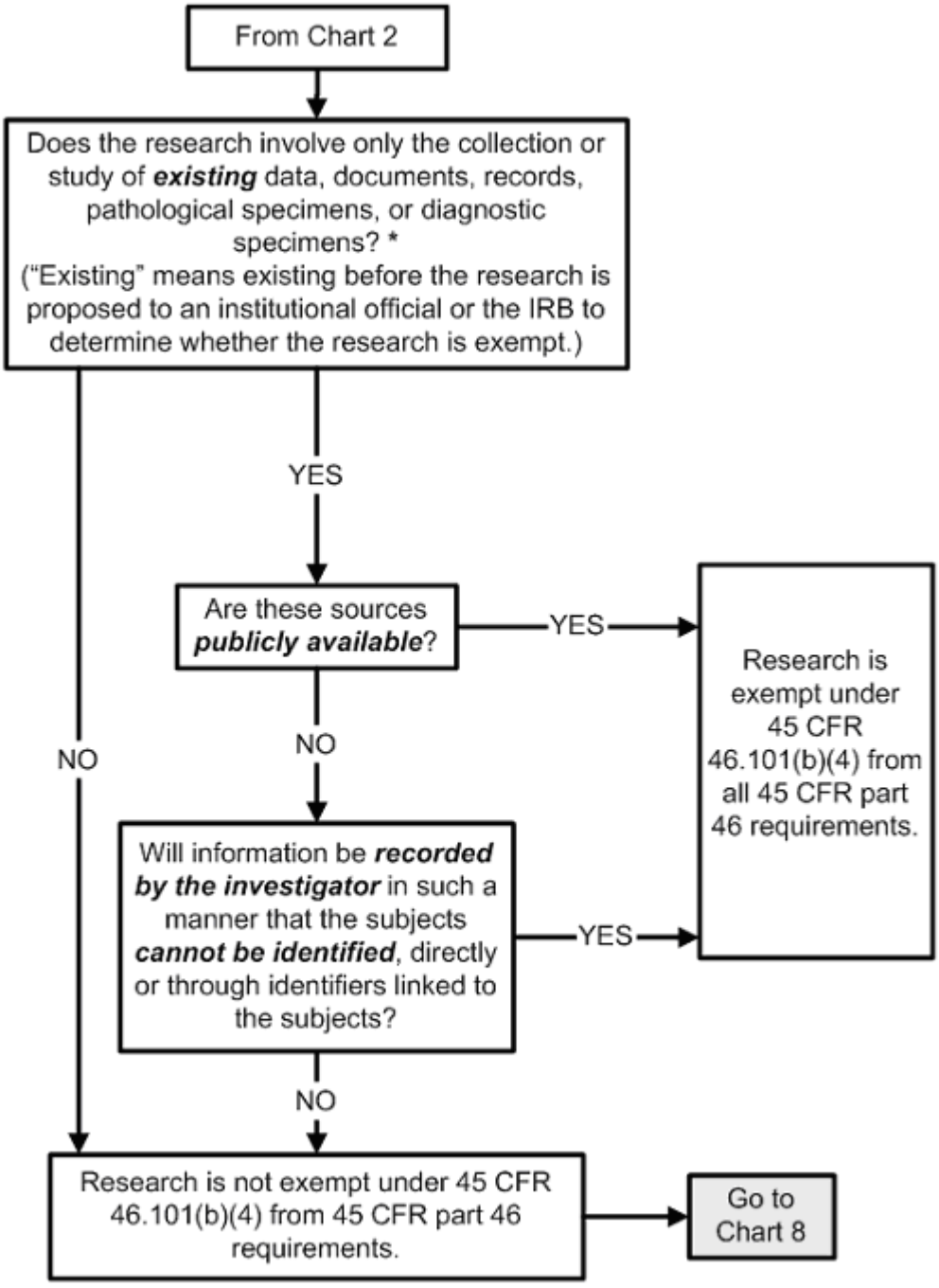
Chart 5: Does Exemption 45 CFR 46.101(b)(4) (for Existing Data Documents and Specimens) Apply?



* Note: See **OHRP** guidance on research use of stored data or tissues and on stem cells at http://www.hhs.gov/ohrp/policy/index.html#tissues and #stem, and on coded data or specimens at #coded for further information on those topics.

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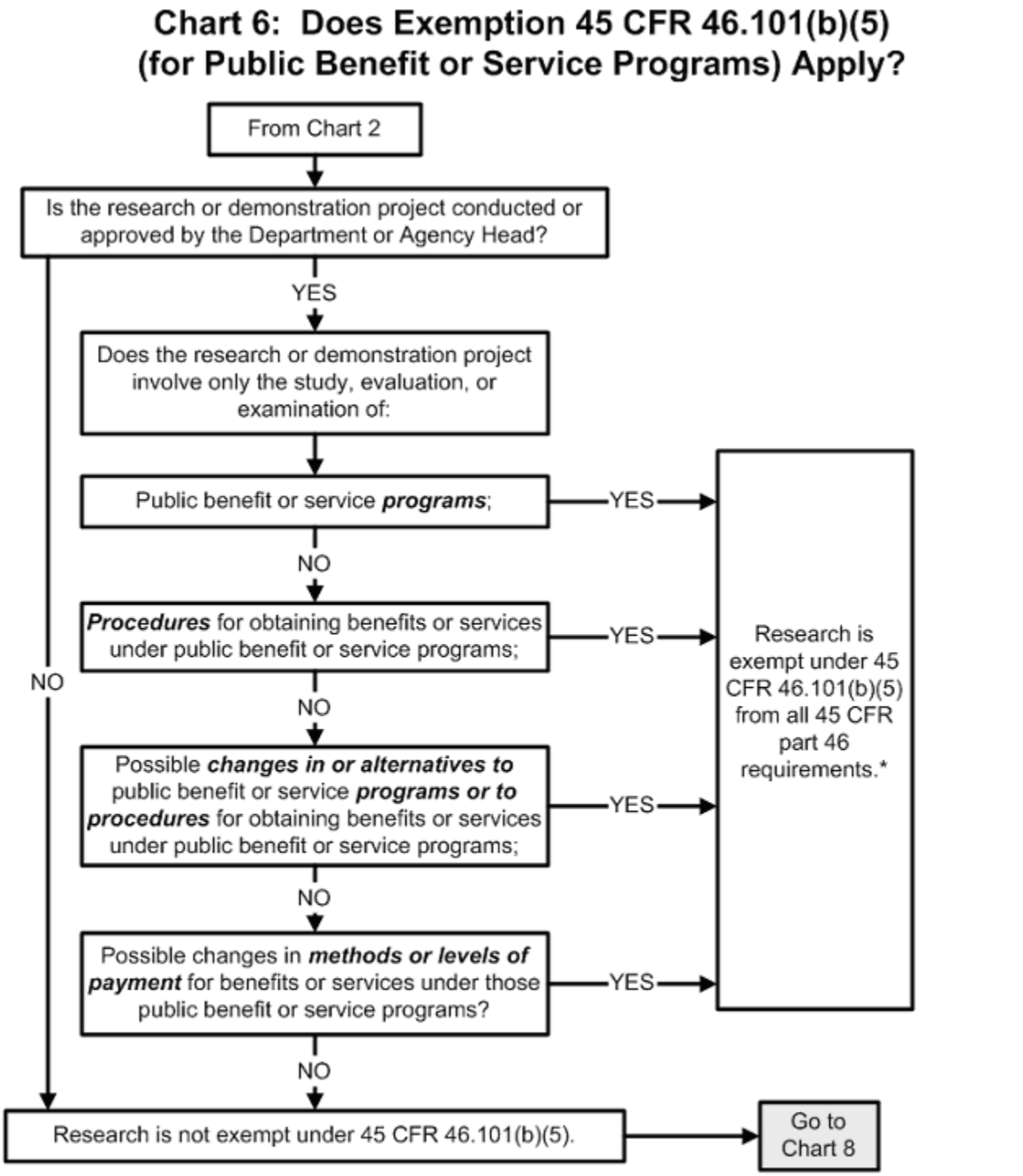

* Note: See **OHRP** guidance on exemptions at http://www.hhs.gov/ohrp/policy/index.html#exempt for further description of requirements for this exemption.

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Chart 7: Does Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies) Apply?

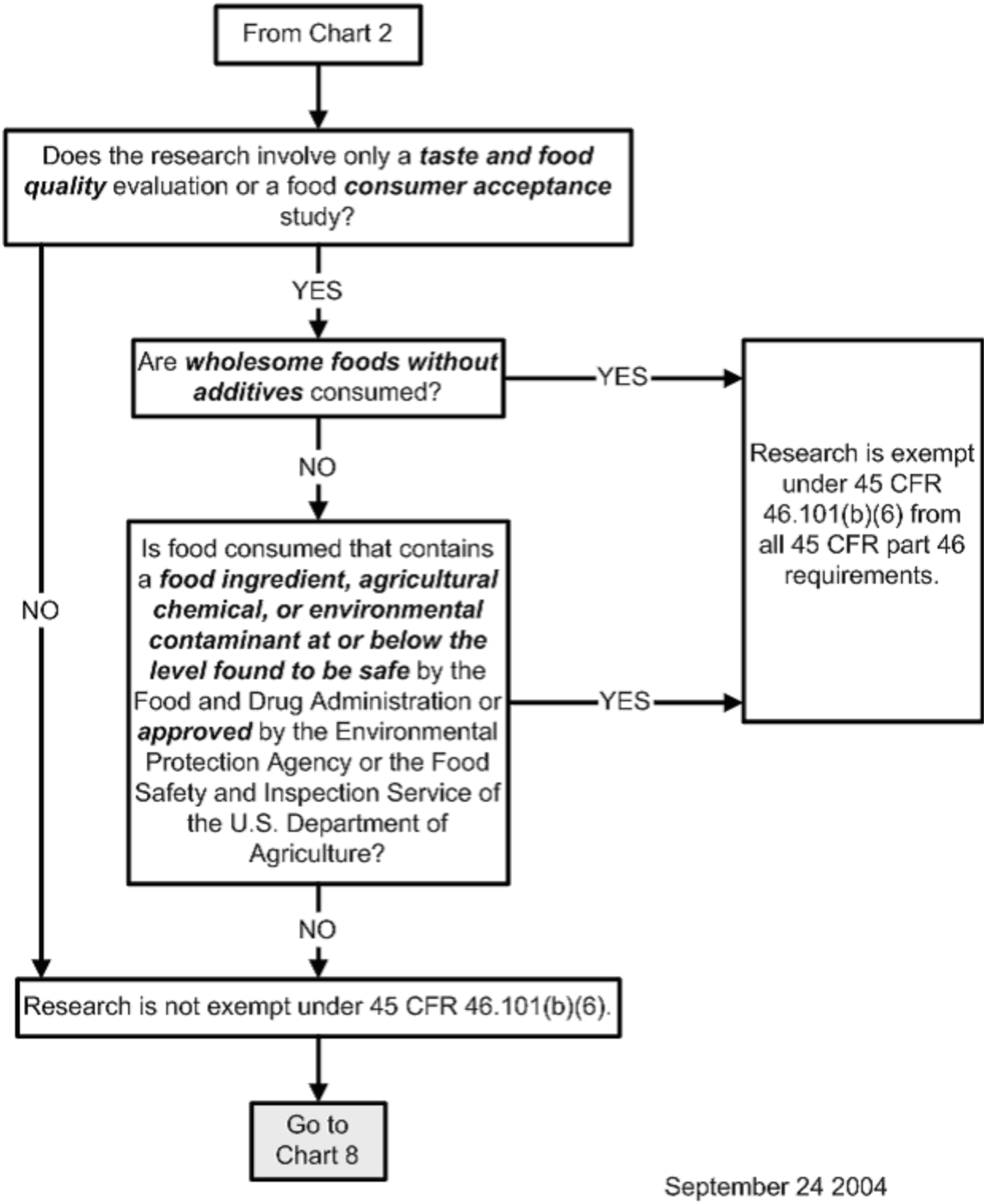

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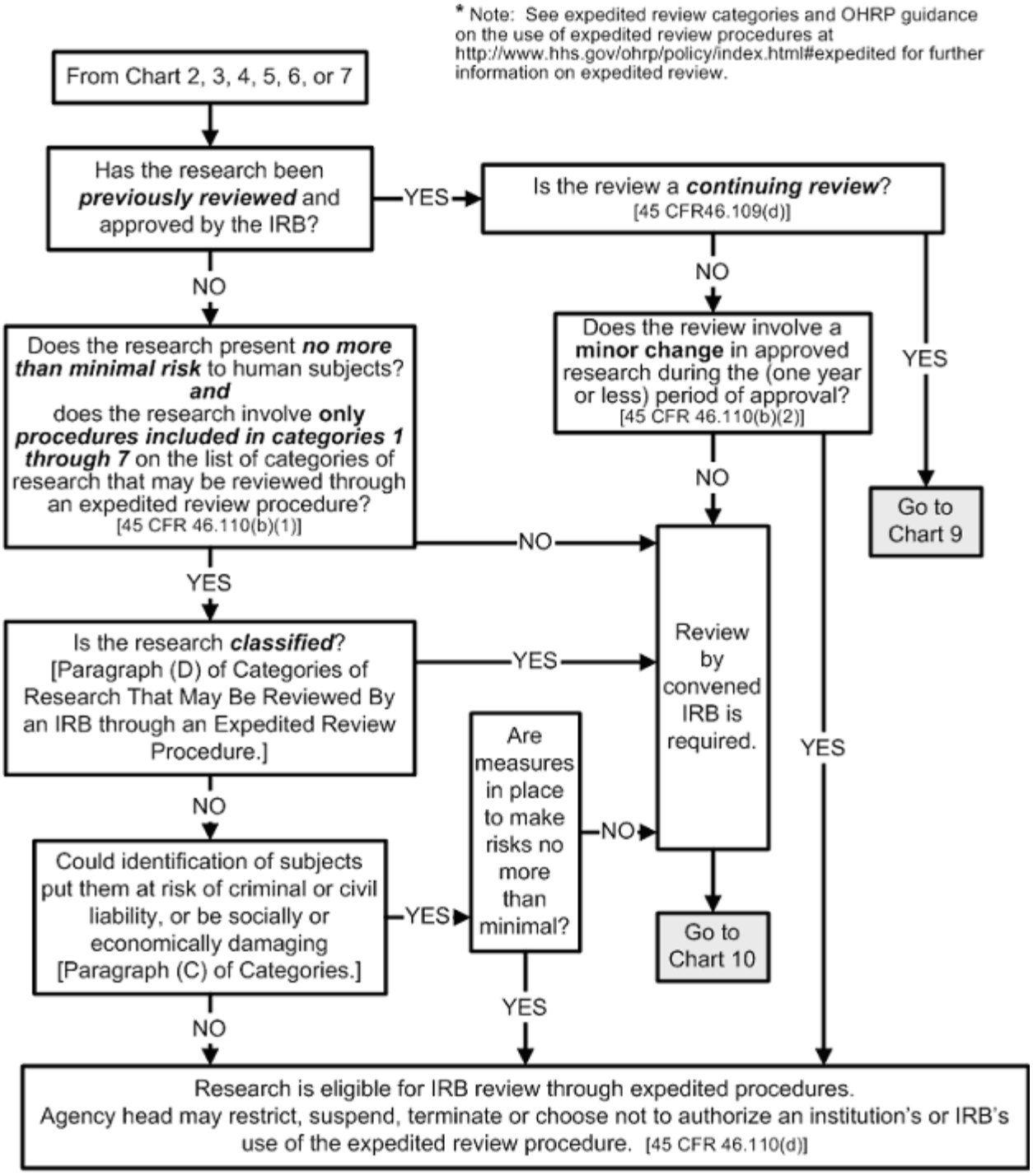
Chart 8: May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?*



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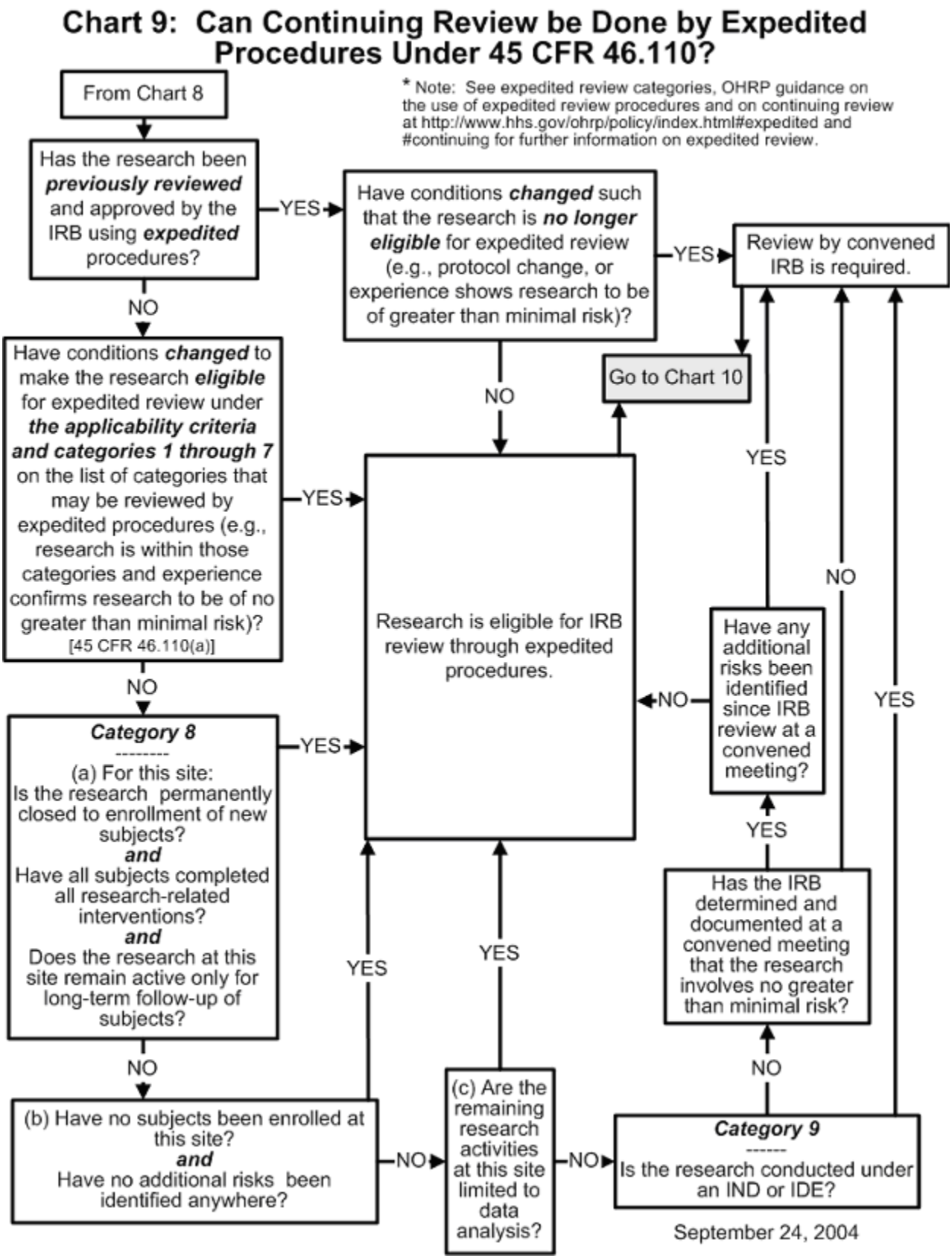
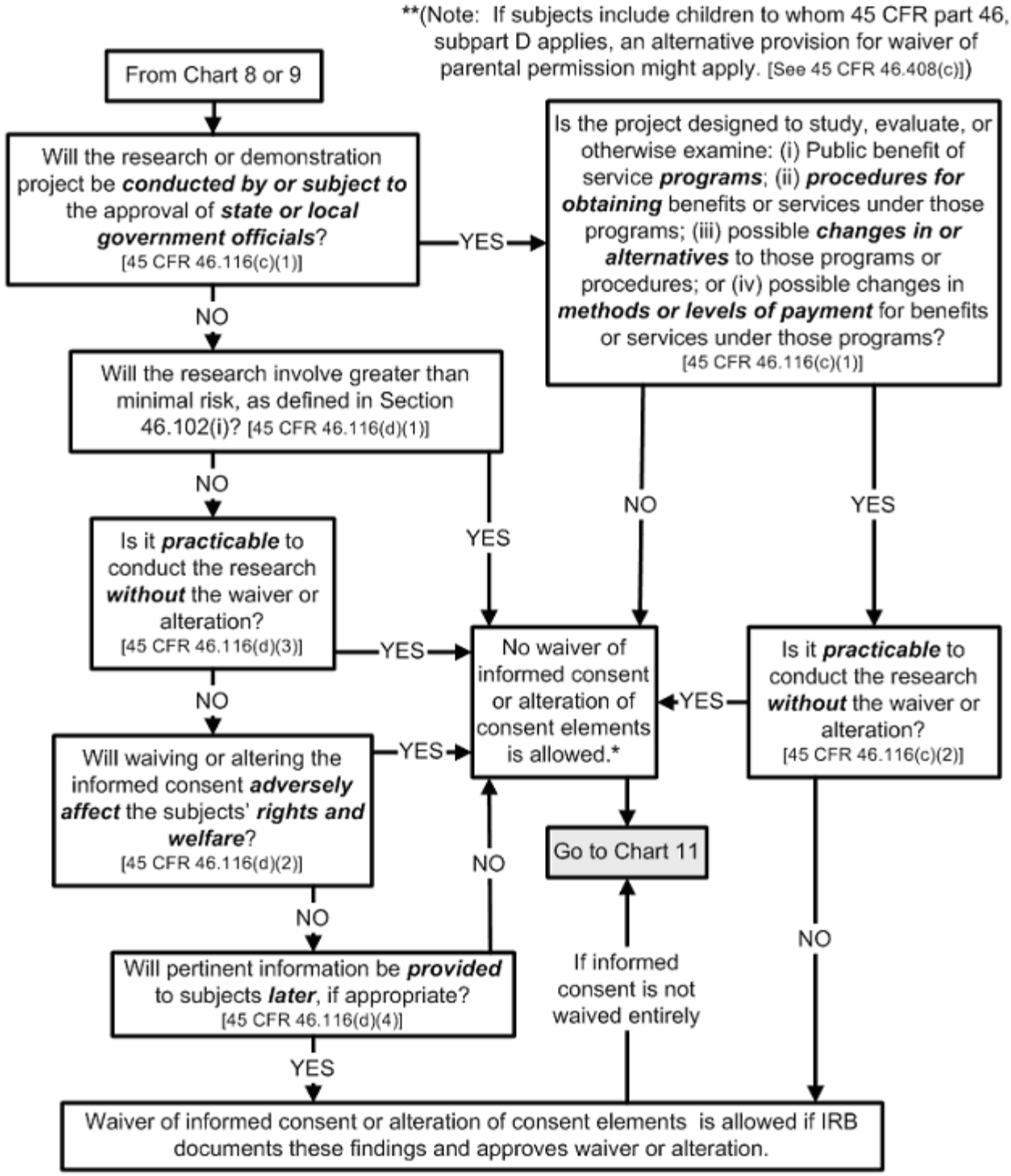


Chart 9: Can Continuing Review be Done by Expedited Procedures Under 45 CFR 46.110?
From Chart 8
* Note: See expedited review categories, OHRP guidance on the use of expedited review procedures and on continuing review at http://www.hhs.gov/ohrp/policy/index.html#expedited and #continuing for further information on expedited review.
Has the research been previously reviewed and approved by the IRB using expedited procedures?
YES
Have conditions changed such that the research is no longer eligible for expedited review (e.g., protocol change, or experience shows research to be of greater than minimal risk)?
YES
Review by convened IRB is required.
NO
Have conditions changed to make the research eligible for expedited review under the applicability criteria and categories 1 through 7 on the list of categories that may be reviewed by expedited procedures (e.g., research is within those categories and experience confirms research to be of no greater than minimal risk)? [45 CFR 46.110(a)]
NO
Go to Chart 10
YES
Research is eligible for IRB review through expedited procedures.
Category 8
(a) For this site: Is the research permanently closed to enrollment of new subjects? and Have all subjects completed all research-related interventions? and Does the research at this site remain active only for long-term follow-up of subjects?
YES
NO
(b) Have no subjects been enrolled at this site? and Have no additional risks been identified anywhere?
NO
(c) Are the remaining research activities at this site limited to data analysis?
NO
Category 9
Is the research conducted under an IND or IDE?
YES
NO
Has the IRB determined and documented at a convened meeting that the research involves no greater than minimal risk?
YES
NO
Have any additional risks been identified since IRB review at a convened meeting?
YES
NO
YES
YES
YES
September 24, 2004

Chart 10: Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?**



* Note: See OHRP guidance on informed consent requirements in emergency research at http://www.hhs.gov/ohrp/policy/index.html#emergency for further information on emergency research informed consent waiver.

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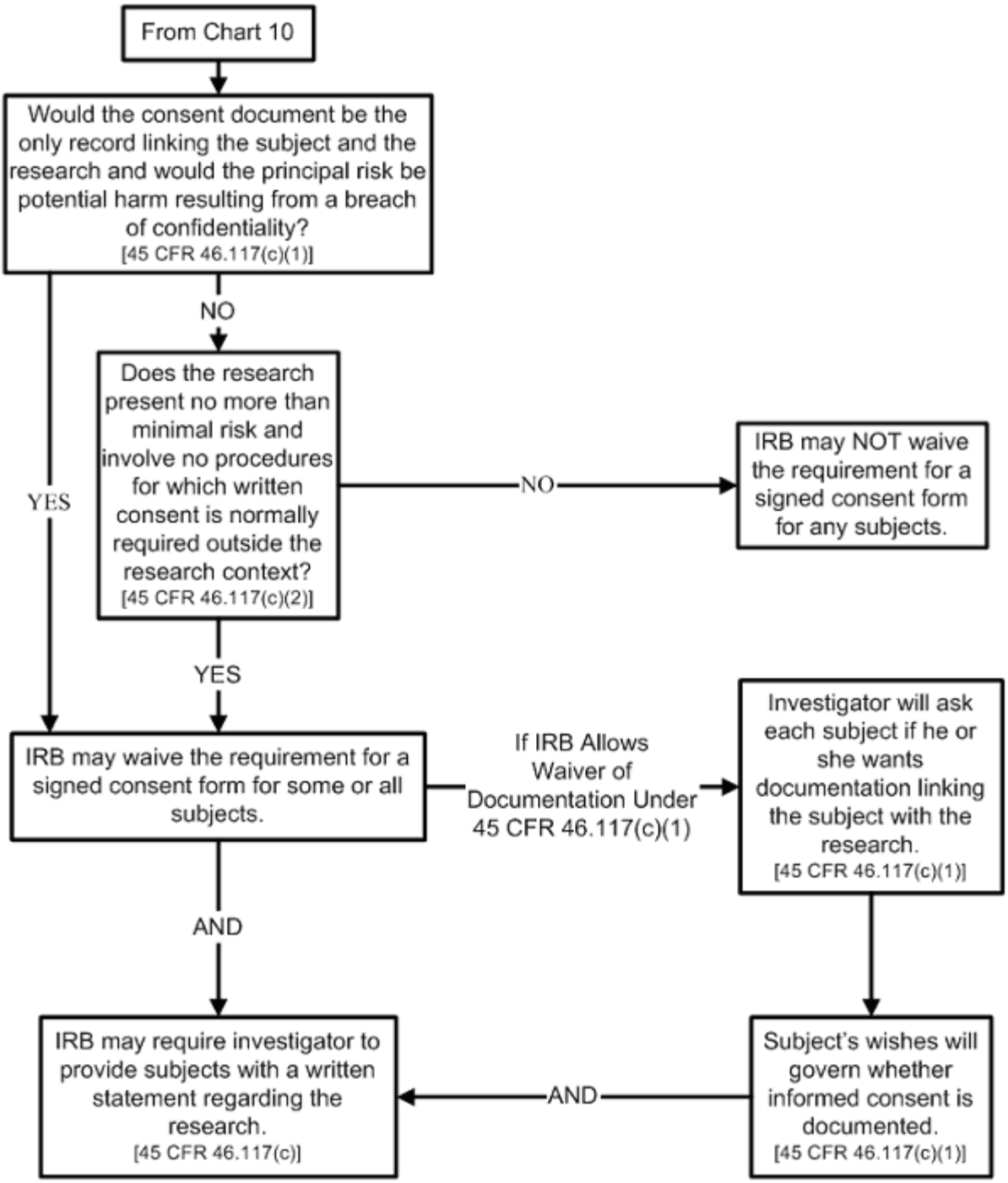
Chart 11: Can Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?



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