

# Chapter 14: Vulnerable Subject Populations

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## Chapter 14

# Vulnerable Subject Populations

This chapter addresses additional protection required when “vulnerable subjects” participate in research. Children, pregnant women, fetuses, neonates, and prisoners are vulnerable subjects as stated in the federal regulations (45 CFR 46 Subparts [B](#), [C](#), and [D](#)).

IRBs and researchers must be aware of “vulnerability” beyond the regulatory definitions. Individuals and classes of subjects may also be vulnerable depending on the research, the situation, their condition and susceptibility to coercion. Researchers are expected to take special precautions when including individuals who have a compromised ability to understand and/or are vulnerable to coercion.

### 14.1 Protection of Children Involved as Subjects in Research (45 CFR 46 Subpart D)

State and federal regulations use different terms to describe individuals below the age of consent. Federal human research regulations refer to “children”. California laws use both “minor” and “child” to refer to people under 18.

#### *Definitions Related to Children as Research Subjects*

<b>Children</b>	Individuals who have not attained the legal age to consent to research treatments or procedures. In California, the legal age is 18 years of age but there are exceptions which allow individuals under the age of 18 to consent to research and some medical procedures
<b>Minors</b>	Individuals under 18 years of age (CFC 6500)
<b>Assent</b>	A child's affirmative agreement to participate in research. Failure to object should not be construed as assent (45 CFR Part 46.402)
<b>Guardian</b>	An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care (45 CFR Part 46.402). In California, a guardian may be a parent, a legally appointed guardian, a guardian <i>ad litem</i> as appointed by a court (this is an individual who may have no relationship to the minor who is appointed by the court to protect and represent the interests of the minor before the court), or others as

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	consistent with an order of a court having jurisdiction over the minor. For wards of a court, usually an order from the judge is required in addition to permission from the person charged with care of the child
<b>Parent</b>	A child's biological or adoptive guardian
<b>Permission</b>	The authorization of parent(s) or guardian(s) to the participation of their child or ward in research
<b>Ward</b>	An individual (usually a minor) who the court has appointed a guardian to care for and take responsibility for that individual. If the minor is suffering from parental neglect or abuse, or has been involved in trouble with the law, a government agency may take temporary custody of the minor for their protection. If the custody is court-ordered, the child is a "ward of the court" or a "ward of the state."
<b>Legally Authorized Representative</b>	An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research

### Permissible Research with Children

To involve children in research, direct or indirect benefit must justify the risk level. The disease or condition to be studied must be related to a research need in children that cannot be satisfied in an adult population. The information below describes the four permitted categories of research with minors defined by federal regulation ([45 CFR 46, Subpart D](#)). If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of the section for additional DOD regulations.

### Permitted Categories for Research with Children

Category	Risk-benefit	Parental Permission Requirements
<b>Category 1</b> ( <a href="#">45 CFR 46.404, 21 CFR 50.51</a> )	<b>Minimal Risk</b> <ul style="list-style-type: none"> <li>Research not involving greater than minimal risk</li> <li>Permission from ONE parent/legal guardian may be sufficient. Assent may be required if</li> </ul>	One parent/legal guardian <b>may</b> be sufficient

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	<p>child is 7 years of age or older</p> <ul style="list-style-type: none"> <li>• <u>Usually subject to</u> Expedited level of review</li> <li>• Example: A study involving one venipuncture (no more than the lesser of 50 ml or 3 ml per kg in an 8-week period) in healthy 10-year-old subjects</li> </ul>	
<p><b>Category 2</b> (<a href="#">45 CFR 46.405, 21 CFR 50.52</a>)</p>	<p><b>Greater than Minimal Risk, Direct Benefit to Subject</b></p> <ul style="list-style-type: none"> <li>• Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects</li> <li>• Permission from ONE parent/legal guardian <i>may</i> be sufficient <b>and</b> assent may be required if child is 7 years of age or older</li> <li>• Usually subject to Full Board review</li> <li>• Example: A Phase II study using an experimental chemotherapeutic regimen for children with malignant brain tumors for whom standard therapy has failed</li> </ul>	<p>One parent/legal guardian <b>may</b> be sufficient</p>
<p><b>Category 3</b> (<a href="#">45 CFR 46.406, 21 CFR 50.53</a>)</p>	<p><b>Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject's Condition</b></p> <ul style="list-style-type: none"> <li>• Research involving minor increase over minimal risk greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subject's disorder or condition</li> <li>• Permission of BOTH parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent may be required if child is 7 years of age or older</li> <li>• Subject to Full Board review</li> </ul>	<p>Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.</p>

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	<ul style="list-style-type: none"> <li>• Example: A study testing new biomarkers of disease progression that involves 2 extra samples of cerebrospinal fluid over a year of therapy (beyond the 5-6 that would be done as part of the child’s routine care.)</li> </ul>	
<p><b>Category 4 –</b> (<a href="#">45 CFR 46.407</a> <a href="#">21 CFR 50.54</a>)</p> <p><i><b>NOTE: A category 4 study is very rarely approved.</b></i></p>	<p><b>Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children’s Health or Welfare</b></p> <ul style="list-style-type: none"> <li>• Research not otherwise approvable which presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children</li> <li>• The Secretary of the U. S. Department of Health and Human Services, after consultation with a panel of experts and following an opportunity for public review and comment, must either approve or deny approval of the study.</li> <li>• Permission of BOTH parents/legal guardians is required, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent of child (if child is 7 years of age or older).</li> <li>• Subject to Full Board review and DHHS review as described above</li> <li>• Example: A study examining sleep mechanisms in children to better understand sleep-related diseases. Involves 13- to 17-year-old adolescents undergoing 3 hospital visits for IV infusion of acetate and glucose followed by MRI, in normal and sleep-deprived groups. [See OHRP’s “Special Protections for Children as Research Participants” for more information about the above and other examples of the handful of</li> </ul>	<p>Both parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.</p>

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	studies reviewed in this category nationwide]	
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### Permission from Parents and Assent from Children

The term permission refers to legally binding authorization granted by parents or guardians. In most cases, permission from one or both parents/guardians must be obtained for their child/ward to participate in a research study. Circumstances in which parental permission may be unnecessary or inappropriate are discussed below under Waiver of Parental Permission.

For children/subjects, the term used is *assent*. Typically, children do not have the legal capacity to consent to participate in research, but children should be involved in the process if they are able to assent (capable of having a study explained to them and/or reading a simple form about it, and giving verbal or written agreement if they decide to participate in the study.) Circumstances in which a child's assent may be unnecessary or inappropriate are discussed below under Waiver of Child's Assent.

### Consent Guidelines for Children by Age Group

Age of Participant	Assent Form Recommended	Parental Permission Form Recommended
Infant-6 years old	No	Yes
7-13 years old	Yes	Yes
14-17 years old	Yes	No (add signature line to adolescent assent form for parent(s) to sign)
13-17 years old	Yes	Yes

#### When One Parent's Permission Is Sufficient

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For research that falls into risk-benefit category 1 or 2, the IRB may determine that permission from only **one** parent is sufficient. The IRB will find that permission of one parent is sufficient unless the nature of the study seems likely to provoke disagreements about participation among two parents, in which case permission from two parents may be required unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor.

Research that falls into Category 3 or 4 requires permission from both parents, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child [[45 CFR 46.406](#), [45 CFR 46.407](#), [21 CFR 50.55\(e\)](#)].

When there is only one living parent or guardian or one parent has sole custody after a divorce, the PI may determine that single-parent or single-guardian permission is sufficient.

### **When Parents Disagree**

If parents disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. Even if only one parent's signature is required, when both parents are involved in the decision, they must agree for the child to be enrolled.

## **Waiver of Parental Permission**

In certain cases, parental permission is not a reasonable requirement to protect subjects (neglected or abused children); more detailed examples are given below. The IRB will consider requests for waiver of parental permission on a case-by-case basis. For non-FDA-regulated studies, the IRB may waive parental/guardian permission provided “an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law” ([45 CFR 46.408](#)).

Additionally, Public Demonstration Projects may obtain a waiver of parental permission if the IRB finds that all criteria below are satisfied:

- The research is to be conducted by or subject to the approval of state or local government officials, and

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- The research is 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, and
- The research could not practicably be carried out without the waiver or alteration, and
- The research is not FDA-regulated.

**NOTE: Parental Permission for children’s enrollment cannot be waived for FDA-regulated studies except for the use of an FDA test article meeting the emergency exception.** The FDA regulations do not contain a provision for waiver of parental permission.

### **Examples where parental permission *may* be waived:**

- Research on child abuse or neglect, or research that is reasonably likely to elicit information identifying child abuse or neglect, where there is serious doubt as to whether the parents’ interests reflect the child’s interests [[45 CFR 46.408\(c\)](#)].
  - The Federal Regulations specifically refer to “research on neglected or abused children” as an instance where “parental or guardian permission is not a reasonable requirement to protect the subjects,” the IRB would be likely to waive parental permission in such a case, provided the other requirements of the regulations [[45 CFR 46.408\(c\)](#)] are met.
- Research on people under age 18 who are in circumstances where they are clearly outside of parental influence or control.
  - Researchers also should be aware that some people under 18 who are living independently may not fit the federal definition of “children” and are able to consent for themselves without a waiver of parental permission. See [California Exceptions Permitting Certain Minors to Consent](#) below.

### **Examples where parental permission may *not* be waived:**

- Research on parental political affiliations or beliefs
- Research on mental or psychological problems, sexual behavior or attitudes, illegal, antisocial, or self-incriminating behavior; religious affiliations or beliefs

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- Research on appraisals of other individuals with whom the minor has a familial relationship
- Research on relationships legally recognized as privileged (lawyers, doctors, clergy)

### Waiver of Child Assent

In certain cases, the IRB may waive the requirement to obtain children's assent, for example:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted, or
- The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research ([45 CFR 46.408](#), [21 CFR 50.55](#))

The parents' right to make medical decisions for their child may come into conflict with the child's right to give or withhold assent. In this situation, assent may not be mandatory, though it always should be sought.

The IRB's decision about waiver of assent will depend on the specifics of the study. For example, assent would likely be waived for a trial of primary induction therapy for a new malignancy where there is a real prospect of direct benefit to subjects. Waiver of assent would be less likely for a recurrent brain tumor study if direct benefit is not probable. The IRB would want to ensure that the child could refuse to participate.

If the child is considered capable of being involved in the informational process, a simple verbal explanation of what will happen to him/her and the opportunity for questions and discussion should always be provided. Even if the requirement for assent is waived, it is always preferable to seek the child's assent if possible. There must be documentation on the parental permission form or in the study records that the child was appropriately informed about the study.

### Children under Guardian Care

In California, a guardian normally has the same authority with respect to the child as a parent having legal custody, except as limited by statute or court order (the legal

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document establishing the guardianship). This includes the authority to consent on behalf of the child to general medical care.

For research that involves medical care, however, a guardian's authority to consent or require is restricted, in the absence of an affirmative court order, in the following circumstances:

- By the terms of any letters of guardianship issued by a court (a certified copy of which should be obtained and placed in the medical record)
- For surgery on a child 14 years or older, unless:
  - The child also consents;
  - The guardian obtains a court order, or
  - The guardian has determined based on medical advice that an emergency exists in which the child faces loss of life or serious bodily injury if the surgery is not performed.
- From administering an “experimental drug” (defined in Health & Safety Code Section 111515; FDA investigational drug), unless a 7 years or older child also consents and the drug is related to maintaining or improving health or obtaining information about a pathological condition of the child
- From authorizing electro-convulsive treatment (defined in [Welfare & Institutions Code Section 5325](#))
- From admitting the child to a “mental health treatment facility” [defined in [Probate Code 2356\(a\)](#)] without the child's consent
- From authorizing antipsychotic drugs except under certain circumstances
- From authorizing an elective procedure performed primarily for the purpose of rendering the child sterile (not treatment which secondarily results in sterilization)
- From authorizing psychosurgery under any circumstances

For additional information regarding informed consent considerations, refer to “[Informed Consent for Children Not in Parental Custody](#)” below.

## Children under the Jurisdiction of Dependency Court / Court Appointee

Parental permission and consent for a child’s participation in research is not required when the juvenile dependency court has explicitly removed the individual parents’ power to make such a decision. In cases where the parent has lost parental rights, the IRB can accept consent from whomever the court appoints as authorized under applicable state or local law to consent on behalf of a child to general medical care.

NOTE: The court cannot issue “blanket consents” even if the court rules allow the court to issue an order allowing the conduct of research including access to juvenile records. To the extent that a court order has been interpreted as “blanket consent,” the IRB should not accept it as such because this mechanism does not adequately protect child subjects.

Special considerations apply to research involving children who are wards of the state. Investigators should contact the IRB staff or the Office of Compliance if they need further guidance.

The IRB may approve a protocol that involves wards and research involving greater than minimal risk but presenting the prospect of participant direct benefit (under 45 CFR 46.406 or 21 CFR 50.53) or not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (under 45 CFR 46.407 or 21 CFR 50.54) only if:

- The research is:
  - Related to their status as wards, or
  - Conducted in schools, camps, hospitals, Institutions, or similar settings in which the majority of the participating children are not wards, and
- The research appoints an advocate for each child, who:
  - May be the same individual for all of the children
  - Has the background and experience to act in (and agrees to act in) the best interest of the child for the duration of the research, and
  - Is not associated in any way with the research (except as an advocate), the investigators, or any guardian association

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Additionally, for research involving medical care for wards of a court, often an order from the judge is required, in addition to permission from the person charged with the care of the child.

Before waiving the parental consent requirement, the IRB should require a court order that clearly and specifically provides that the children may participate in research without parental consent. According to [California Welfare and Institutions Code Section 361 \(a\)](#) there is no limitation of parents' right to consent to research that was not "necessary to protect the child."

### Informed Consent for Children Not in Parental Custody

Investigators are required to obtain a court order permitting the participation of the individual subjects in the research without parental consent, and should be required to follow the procedure in [Los Angeles County Superior Court Rule Chapter 7](#) (if research and the children are within Los Angeles County) or other applicable court procedures.

The investigators are required, if possible, to obtain written permission from each parent unless it meets the requirements for waiver of parental consent, then from each subject's guardian unless the IRB determines that such permission need not be obtained in accordance with federal human subjects regulations.

The investigators are required to obtain the assent of subjects unless the IRB determines that assent should not be obtained in accordance with federal human subjects regulations.

If the study is more than minimal risk, each individual subject must have a court appointed advocate according to [45 CFR 46.405](#) and [45 CFR 46.406](#).

### California Exceptions Permitting Certain Minors to Consent

In California, minors (those under 18 years of age) generally may not consent to medical care or treatment, or research involving medical care or treatment, without a parent or legal guardian's consent. Federal regulations when interpreted with California legal exceptions allow minors, as described below, to consent as adults to research or treatment:

- **Emancipated minors:**

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- married or divorced, or
- on active duty in the U.S. armed forces
- emancipated by a court
- have the legal right to consent on their own behalf to medical, dental, or mental health treatment. They also have extensive other rights to enter into legal and business arrangements, and so can consent to be included in other research (such as surveys or interviews) ([Section 7000-7143](#))

The IRB interprets California law relating to emancipated minors as authorizing an emancipated minor to give consent to participation in any type of research, even if the research does not involve treatment.

- **Self-Sufficient minors:**
  - 15 years of age or older, and
  - living separate from their parents/guardians, and
  - managing their own financial affairs
  - may consent to the minor's own medical or dental care (Section 6922)
- **Care related to the prevention or treatment of pregnancy**
- **Minors, 12 years or older, seeking care for:**
  - Out-patient mental health treatment or counseling, excluding drugs
  - Care related to the diagnosis or treatment of reportable infectious, contagious, or communicable/sexually transmitted diseases
  - Care provided to the victims of sexual assault or rape
  - Medical care and counseling relating to the diagnosis and treatment of drug or alcohol abuse (only if treating physician deems and documents that parental involvement is inappropriate), excluding narcotic replacement drugs.

With IRB approval, for the above categories a minor must provide consent and sign the consent form just as an adult would, unless the IRB approves a waiver or alteration of the

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usual consent standards for adults. The IRB requires that any investigator that is not familiar with these laws and proposes to enroll a minor without parental permission to contact the IRB staff for further guidance. The IRB always retains the option to exclude minors that may otherwise consent in light of risks or the nature of the trial.

Researchers enrolling participants in other states or countries must comply with local law. In all cases, if the prospective subjects cannot legally consent for the treatments or procedures involved in the study because they are too young, they are considered "children" by federal regulations. If they can consent for the treatments or procedures, they are not "children" by federal regulations (therefore if they are not “children” 45CFR46 subpart D does not apply).

### Discovery and Disclosure of Sensitive Information

In the course of research investigators may discover sensitive information about subjects that is not directly related to the study aims.

Examples of such information include sexual activity, STDs, use of illegal substances, HIV status, cancer, and child abuse. Investigators need to consider how they will handle disclosure of such situations should they arise. The permission and/or assent form should describe plans for disclosure—or non-disclosure—of such information to parents, legal authorities, and the subjects themselves.

In some cases, it may be appropriate for the PI to seek an NIH Certificate of Confidentiality (refer to [Section 11.4 – Certificate of Confidentiality](#)).

Also visit <http://grants.nih.gov/grants/policy/coc/background.htm> for information as to whether a certificate is applicable for a particular study.

### Mandatory Reporting

Discovery of child abuse initiates certain ethical and legal obligations. In most cases, the same reporting expectations pertain in research settings as in clinical settings. University researchers may be health professionals or other “mandated reporters” under the California Child Abuse and Neglect Reporting Act ([California Penal Code 11164-11174.3](#)). Even if the mandated reporter status is not clear, the investigator can make a voluntary report to the appropriate agency.

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If an investigator is planning a study that is designed or likely to elicit information about sexual or physical abuse of a child, the application and consent/assent forms must indicate how discovery of such information will be handled.

If such information is discovered unexpectedly (not anticipated given the study design or subject population), the PI should seek advice from his/her department Chair or dean or from the Director of the IRB, who may refer the question to Legal Counsel.

### Enrolling Children in Long-Term Studies

Long-term research studies may involve subjects who are children at the time of enrollment but reach the age of consenting (18 years old, in California) while study procedures or follow-up are still ongoing. The IRB will consider on a study-by-study basis whether obtaining new consent from such subjects is required.

If there is continued interaction with subjects who were first enrolled as children, “re-consenting” when a subject’s legal status changes will usually be required. If the only continuing study procedures are follow-up activities such as review of records or examination of biological specimens, the original consent may suffice.

### Research Involving Children in Educational Settings

When planning studies involving children in educational settings, investigators should consider the following issues:

The first step for investigators is to obtain support from the school principal or administration. This may include contacting school district officials, the local PTA, and/or the principal of a particular school. School officials and/or teachers may approve recruitment for a study, but they do not have authority to give permission for participation of individual children in research—only a parent or guardian, with the child’s assent, can do so.

If the study will be conducted during school hours, an equivalent alternative activity should be offered for students who do not wish to participate.

Additionally, according to [California Education Code 51513](#), generally speaking, no test, questionnaire, survey, or examination containing any questions about the pupil's personal beliefs or practices in sex, family life, morality, and religion, or any questions about the pupil's parents' or guardians' beliefs and practices in sex, family life, morality, and

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religion, shall be administered to any pupil in kindergarten or grades 1 to 12, inclusive, unless the parent or guardian of the pupil is notified in writing that this test, questionnaire, survey, or examination is to be administered and the parent or guardian of the pupil gives written permission for the pupil to take this test, questionnaire, survey, or examination.

### FERPA Rules and Research with Education Records

The Family Educational Rights and Privacy Act (FERPA) (34 CFR 99) sets limits on the conditions under which education records can be accessed for research purposes.

Education records are generally defined in FERPA as personally identifiable information regarding a student in a K-12 or higher education setting that receives federal funding. More specifically, FERPA states that education records may include any of the following items:

records, files, documents, and other materials, such as films, tapes, or photographs, containing information directly related to a student that an educational agency maintains on students in report cards, surveys, and assessments, health unit records, special education records, and correspondence between the school and other entities regarding students (34 CFR 99.3(d))

It is the holder of the records (e.g., a school authority, university registrar) –not the researcher – who carries the legal responsibility for abiding by FERPA. Therefore, it is the holder of the records—not the researcher – who is in violation of FERPA if education records are released inappropriately or illegally.

It is not the responsibility of the IRB to ensure that researchers access personally identifiable student level data in compliance with FERPA. It is incumbent upon the holder of the records to ensure that the personally identifiable information was released pursuant to the conditions imposed by FERPA. Moreover, it is up to the researcher to ensure that the personally identifiable information from an education record will not be disclosed to any other party without prior consent of the parent or eligible student. If a researcher improperly discloses personally identifiable information from an education record, the researcher may not be allowed to access information from education records for five years (34 CFR 99.33(e)). Please see FERPA for more information regarding researcher responsibilities: <http://www.ed.gov/policy/gen/guid/fpco/ferpa/index.html>.

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FERPA requires that the holder of the records ensure written consent is obtained from a parent or eligible student in order to release personally identifiable student information. The holder of the record only obtains consent from parents and eligible students under limited circumstances (see the Directory Information Policy exception below). Consequently, record holders do not have consents on file for the release of most information contained in the education record. This means that a researcher who is interested in obtaining personally identifiable information from a student's education record must obtain written consent from the parent or the eligible student if he/she wants to access personally identifiable student information from a record holder (K-12 school or district and institutions of higher education).

There are two exceptions to FERPA that might also enable a researcher to access personally identifiable student information without obtaining consent from the parent or eligible student. The holder of the record *may* release the records to the researcher under the following conditions:

- The researcher is conducting studies *for or on behalf* of the school or district (34 CFR 99.31(a)(6))
- The information is identified by the school within its Directory Information policy (34 CFR 99.31(a)(11))

If a researcher has entered into a formal agreement with the holder of the record(s) to conduct research on the record holder's behalf, consent is not required in order for personally identifiable information to be shared with the researcher.

If the researcher is requesting personally identifiable information that has been designated by the holder of the record as "Directory Information," the holder of the record may decide to release this information without obtaining additional consents. Directory Information is information that has been deemed under FERPA to not pose a risk to the student if released. Consent is obtained by the record holder on a yearly basis for the release of this information. Information that is usually considered directory information includes the student's name, date of birth, dates of attendance, and other information that has been deemed harmless pursuant to FERPA (see each school's Directory Information policy for more information). Although the record holder *may* release this information under the Directory Information exception, the record holder does not have to do so.

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Finally, consent is not required if the information requested for release is not personally identifiable (therefore has been stripped of any identifying information).

Individuals who are employed by schools or universities in one role (e.g., teacher, administrator, superintendent, academic advisor) and who are conducting research as part of their graduate level coursework (e.g., masters thesis or dissertation) must abide by FERPA when seeking to access personally identifiable student information. In other words, for the purposes of accessing student information *as a researcher*, they must ensure that they seek parent or eligible student consent or that they are able to access the information as the result of one of the aforementioned exceptions. They may not use their access through their employment in order to obtain personally identifiable information.

### **PPRA Role in Research Supported by Department of Education**

USC Office of Compliance and outside legal counsel have determined that there is no IRB role in applying PPRA to human subjects research. Complying with PPRA is the responsibility of the school system/district (per internal communication dated 3/20/14).

It is the responsibility of the researcher/school that research funded by the Department of Education complies with additional protections under the Protection of Pupil Rights Amendment (PPRA) (34 CFR Part 98).

Schools and contractors must obtain prior written parental consent before minor students are required to participate in any survey, analysis, or evaluation funded by the Department of Education.

### **Research Supported by the Department of Defense (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart D with the following modification:

- The DOD does not apply Subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DOD supported research.

## 14.2 Pregnant Women, Fetuses and Neonates in Research (45 CFR 46 Subpart B)

Federal regulations mandate that IRBs require additional safeguards before approving research involving pregnant women, human fetuses, neonates of uncertain viability, or non-viable neonates. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

### Research Involving Pregnant Women or Fetuses

Pregnant women or fetuses may be involved in research if all of the following conditions are met ([45 CFR 46.204](#)):

- a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses
- b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means
- c) Any risk is the least possible for achieving the objectives of the research
- d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A
- e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A, except that the father's consent need

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not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest

- f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate
- g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D
- h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy
- i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, and
- j) Individuals engaged in the research will have no part in determining the viability of a neonate

### Research Involving Neonates

- a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met ([45 CFR 46.205](#)):
  1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
  2. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
  3. Individuals engaged in the research will have no part in determining the viability of a neonate.
  4. The requirements of paragraph (b) or (c) of this section have been met as applicable.

- b) **Neonates of Uncertain Viability**

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

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1. The IRB determines that:
  - i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
  - ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research, and
2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

### c) Nonviable Neonates

After delivery, nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained
2. The research will not terminate the heartbeat or respiration of the neonate
3. There will be no added risk to the neonate resulting from the research
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means
5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either

or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

### **ViabLe Neonates**

- d) A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D.

#### **§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.**

- a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
- b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of 45 CFR 46 are applicable.

#### **§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.**

DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

- a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
- b) The Secretary of HHS, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:
  - 1. That the research in fact satisfies the conditions of §46.204, as applicable;
  - or

2. The following:
  - i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
  - ii. The research will be conducted in accord with sound ethical principles, and;
  - iii. Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts.

### **Newborn Dried Bloodspots**

The Newborn Screening Saves Lives Reauthorization Act of 2014 explicitly states that the use of newborn dried bloodspots for research is considered to involve human subjects if the research is federally supported and the bloodspots are collected on or after March 18, 2015. The identifiability (or not) of the bloodspots is irrelevant. In other words, if a researcher is receiving de-identified or anonymous bloodspots for research, the research is considered to involve human subjects. A detailed summary of recommendations is provided by the U.S. Department of Health and Human Services, Secretary's Advisory Committee on Human Research Protection (SACHRP). The goal of this recommendation is to provide thoughtful consideration of this act and allow for important research to take place. Refer to: <https://oprs.usc.edu/files/2016/05/SACHRP-Newborn-Dried-Bloodspots.docx>

### **Research Supported by the Department of Defense (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart B with limitations and modifications:

- For the purposes of applying Subpart B risk-benefit analysis, DOD replaces the phrase “biomedical knowledge” with “generalizable knowledge”
- The DOD limits the applicability of Subpart B to research involving:

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- Pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or fetus;  
or
- Fetuses or neonates as participants
- Fetal research must comply with the [US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g](#)

Refer to [Section 3.2 – Research Supported by the Department of Defense](#) for additional DOD requirements.

### 14.3 Prisoners in Research (45 CFR 46 Subpart C)

Because incarceration affects a person's ability to make a truly voluntary decision whether or not to participate in a research project, state and federal regulations provide additional safeguards for the protection of prisoners in research. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

Research involving prisoners is never exempt from IRB review. Any study that recruits prisoners that does not qualify for expedited review must be reviewed at a fully-convened IRB meeting with a prisoner representative present for the discussion and vote of that study protocol. The IRB Chair and/or IRB Director, and/or IRB Staff ensure a prisoner representative and/or consultant will be present at the meeting.

Apart from their membership on the IRB, the majority of the IRB members (exclusive of prisoner representative) shall have no association with the prison(s) involved in the research being reviewed. If research activities under the jurisdiction of the USC IRB involve prisoners held outside of the state of California the investigator is responsible for identifying and ensuring compliance with the laws of that state.

### Additional PI Responsibilities

Under [28 CFR 512](#) the Federal Bureau of Prisons places special restrictions on research that takes place in the Bureau of Prisons. The regulations specify additional requirements that must be addressed by the PI to obtain approval for Bureau of Prison based research.

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The California Department of Corrections and Rehabilitation (CDCR), [Title 15](#), (California Code of Regulations) requires that research that takes place in the department facilities be submitted by the PI to the departments research advisory committee for review and approval.

It is the investigator's responsibility to identify and meet these requirements.

### **Federal Regulations Permit 5 Categories of Research with Prisoners ([45 CFR 46.306](#))**

The 5 permitted categories are:

- i. Studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects
- ii. Studies of prisons as institutional structures or of prisoners as incarcerated persons provided that the study presents no more than minimal risk and no more than inconvenience to the subjects
- iii. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of HHS (through OHRP) has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of their intent to approve such research
- iv. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research

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- v. Waiving the applicability of [45 CFR 46.305\(a\)\(1\)](#) and [45 CFR 46.306\(a\)\(2\)](#) for certain research conducted or supported by HHS. This is referred to as the **Epidemiology Waiver**. In specific, for HHS conducted or supported research involving epidemiologic studies: (1) In which the sole purposes are (i) To describe the prevalence or incidence of a disease by identifying all cases, or (ii) To study potential risk factor associations for a disease, and (2) Where the Institution responsible for the conduct of the research certifies to OHRP, acting on behalf of the Secretary, that the IRB approved the research and fulfilled its duties under [45 CFR 46.305\(a\)\(2\)-\(7\)](#) and determined and documented that (i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and (ii) Prisoners are not a particular focus of the research. (For more information, refer to: <http://www.gpo.gov/fdsys/pkg/FR-2003-06-20/html/03-15580.htm>)

The informed consent form must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on their duration of incarceration or terms of parole. The IRB must determine whether assent is a requirement for research pertaining to prisoners that are children.

### **IRB Considerations for Prisoner Subjects (45 CFR 46.305)**

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find:

1. The research under review represents one of the categories of research permissible under [45 CFR 46.306\(a\)\(2\)](#).
2. Any possible advantages accruing to the prisoner through their participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that their ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers

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4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project
5. The consent information is presented in language which is understandable to the subject population
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on their parole
7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences. Subjects must be adequately informed of this fact.

If the research is conducted or supported by HHS, the University must certify to the HHS Secretary (through OHRP) that the IRB has approved the research under the HHS regulations for research that involves prisoners as participants. Additionally, the HHS Secretary (through OHRP) must determine that the research meets one of the approvable categories before the research can be initiated. This determination is known as the “OHRP Prisoner Research Certification”.

### *Helpful Links*

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- OHRP Guidance on the Involvement of Prisoners in Research:  
<http://www.hhs.gov/ohrp/policy/prisoner.html>
- OHRP Frequently Asked Questions – Prisoner Research:  
<http://answers.hhs.gov/ohrp/categories/1568>

***Definitions Related to Prisoners as Research Subjects***

<b>Prisoner</b>	Any individual involuntarily confined or detained in a penal Institution; individuals sentenced to such an Institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal Institution and individuals detained pending arraignment, trial, or sentencing.
<b>Prisoner Representative</b>	Any individual who can represent the concerns that prisoners might have about research, who has a working knowledge of prison conditions and the life of prisoners, such as an individual employed at a prison, a prisoner chaplain, a social worker who deals with prisoners, or a prisoner advocate
<b>Penal Institution</b>	Any place of confinement for convicted criminals. Penal Institutions include local and county jails and workhouses, reformatories, penitentiaries, prison camps and farms, as well as the modern correctional Institution.
<b>Parolees and Probationers*</b>	<p>Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.</p> <p>Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise about research involving these populations.</p> <p>The Office for Human Research Protection (OHRP), provides specific regulatory definitions for circumstances pertaining to parolees and probationers. The following are examples of application. Refer to <a href="#">OHRP Prisoner Research FAQs</a></p>

**Subjects Who Later Become Incarcerated**

If a study was not initially approved to recruit prisoners, the investigator may not enroll prisoners. A prisoner, who is brought to USC for treatment and happens to be eligible for a research study, may not be enrolled in a study unless: the study was approved to

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include prisoners, and a prisoner representative was present during the discussion and vote of the study.

The regulations for research with prisoners apply to any subject who becomes a prisoner after enrolling in research. It is unlikely that the IRB contemplated the constraints imposed by incarceration during their review therefore, if an investigator determines that a subject has become a prisoner after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or an amendment request must be submitted for the inclusion of prisoners as subjects. With the exception of special circumstances, all research interactions and interventions with, and collection of identifiable private information about, the now-incarcerated subject must cease until all the requirements of [Subpart C](#) have been satisfied. The Office for Human Research Protections (OHRP) guidance allows in special circumstances, for which the Principal Investigator (PI) asserts that it is in the best interest of the subject to remain in the research study while incarcerated; the IRB Chair may determine that the subject can continue to participate in the research until the requirements of [Subpart C](#) are satisfied.

### Limits under California Penal Code

Under the California Penal Code, competent adult prisoners are permitted to decide whether or not to participate in behavioral research, but no biomedical research can be conducted on any prisoner in the state. See [Cal. Penal Code §§ 3501, 3502](#) (also, see definitions for “biomedical” and “behavioral research” at § 3500). Prisoners may, however, obtain investigational drugs or treatments – under a protocol or treatment Investigational New Drug (IND) application – if a physician determines that the drug or treatment is in the best interest of the patient/prisoner and the prisoner gives consent [id. § 3502.5](#). With regard to behavioral research, generally, informed consent must be obtained, but can be waived if it is determined that it would be unnecessary or would significantly inhibit the research [id. § 3505](#). There are specific state law requirements with regard to consent for prisoners, see [id. §3521](#). Additional federal guidelines that pertain to prisoners in research are outlined below. Note, however, that in some instances the federal guidelines conflict with California law.

For more information, review the California Penal Code and guidance links below.

### *Helpful Links*

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- CA Penal Code 3501-3509.5:  
[https://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=2.&article=](https://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=2.&article=)
- CA Penal Code 3515-3520:  
[http://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=3.&article](http://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=3.&article)
- CA Penal Code 3521-3523:  
[https://leginfo.legislature.ca.gov/faces/codes\\_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=4.&article=](https://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=PEN&division=&title=2.1.&part=3.&chapter=4.&article=)
- CA Penal Code 3524  
[https://leginfo.legislature.ca.gov/faces/codes\\_displaySection.xhtml?sectionNum=3524.&lawCode=PEN](https://leginfo.legislature.ca.gov/faces/codes_displaySection.xhtml?sectionNum=3524.&lawCode=PEN)
- CA Code of Regulations, Title 15, Article 9.1 “Research of Inmates/Parolees”  
[http://www.cdcr.ca.gov/Regulations/Adult\\_Operations/docs/Title15-2016.pdf](http://www.cdcr.ca.gov/Regulations/Adult_Operations/docs/Title15-2016.pdf)
- CA Department of Corrections and Rehabilitation (CDCR) guidance “Research Involving Wards, Inmates or Staff”  
[http://www.cdcr.ca.gov/Reports\\_Research/researchWIS.html](http://www.cdcr.ca.gov/Reports_Research/researchWIS.html)
- CA CDCR guidance: “Research Project Approval Guidelines”  
[http://www.cdcr.ca.gov/Reports\\_Research/rpaguide.html](http://www.cdcr.ca.gov/Reports_Research/rpaguide.html)

### **Research Supported by the Department of Defense (DOD)**

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart C with limitations and modifications:

- For research intended to enroll prisoners, the DOD does not allow review by expedited mechanism.

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- If a PI attests that it is in the best interest of a subject who becomes a prisoner to continue participation in the research, the DOD allows the IRB Chair to make a preliminary determination until the convened IRB (and DOD Component, if applicable) can review the request. Otherwise, the IRB may require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB with consultation from the prisoner representative, can review this request to ensure that the rights and well-being of the human subject, now a prisoner, are not in jeopardy.

If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue.

Refer to [Section 3.2 – Research Supported by the Department of Defense](#) for additional DOD requirements.

### 14.4 Cognitively-Impaired Persons

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur during situations associated with high levels of stress (death of a family member). Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally-impaired. Some research questions may be answered only by research that involves persons with impaired decision-making capacity.

Unlike research involving children, prisoners, pregnant women, and fetuses, HHS regulations do not specifically address research involving persons who are cognitively-impaired. While limited decision-making capacity should not always prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population. Subjects with permanent or transient cognitive impairments may find it difficult to understand the difference between research

and treatment, and to differentiate between investigators' multiple roles and interests (practitioner and researcher).

### **IRB Criteria for Reviewing Research with Cognitively-Impaired Persons**

The IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons:

- Research not involving greater than minimal risk
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- The risk is justified by the anticipated benefit to the subjects
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches
- Adequate provisions are made for soliciting the assent of the subject and permission of their legally authorized representative

The IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons when the research is greater than minimal risk, there is no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition:

- The risk represents a minor increase over minimal risk
- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition
- Adequate provisions are made for soliciting assent of the subject and permission of their legally authorized representative

### Assessing Capacity to Consent

A key factor in subjects' decision-making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally. Assessment is complex and there are no standard criteria for determining capacity to consent to research. Individual capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. IRB applications for the proposed involvement of cognitively impaired subjects should propose a plan to screen for incapacity in subjects who are likely to be incapable of providing consent. Assessments should be timed to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Limited decision-making capacity covers a broad spectrum. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation and population. A healthy person in shock may suffer temporarily of impaired decisional capacity, another may have been severely mentally disabled since birth, while a person with schizophrenia may experience fluctuating capacity. Fluctuations in decision-making capacity may require ongoing assessment during the course of research.

### Consenting Cognitively-Impaired Subjects

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject enrolls.

The consent process should be ongoing to ensure subjects' ability understand and follow the protocol. The IRB, at its discretion, may observe the consent process or require an outside witness to observe the consent process.

Investigators are encouraged to review "Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment." (The American Journal of Psychiatry, 155:11, 1998) and, "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity" (The National Bioethics Advisory Commission's report, 1998).

### **Voluntariness, Consent, and Assent**

In addition to determining subjects' ability to consent, investigators must also ensure subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject.

In conclusion, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be necessary in certain circumstances. Treating all individuals who have cognitive deficits as capable, at times, of understanding research is respectful of their autonomy. It also exemplifies the principle of "respect for persons" in The Belmont Report. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

### **Surrogate Consent**

If a potential subject is found to be incapable, the federal regulations allow a "Legally Authorized Representative" to consent on their behalf. The federal regulations leave it to the states to define this term. In California, the selection of an appropriate representative to consent on behalf of those unable to consent for themselves is clearly delineated. The IRB has determined that the individuals defined in the state of California Health and Safety Code, [Section 24178 \(c\) and \(d\)](#), as legally authorized representative meet the HHS and FDA definitions of legally authorized representative. These rules only apply to medical experiments that relate to the cognitive impairment, lack of capacity or serious or life threatening disease or conditions of research subjects.

### **Cognitively-Impaired in Non-Emergency Room Environments**

The research covered is that of medical experiments that "relate to the cognitive impairment, lack of capacity, or serious life-threatening diseases and conditions of research subjects." If a person is unable to consent and does not express dissent or resistance to participation in such research, surrogate informed consent may be obtained

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from a surrogate decision-maker with reasonable knowledge of the subject. The proxy decision maker is to use a “substituted judgment” standard if possible; if not, a “best interests” standard. The proxy shall include any of the following persons, in the following descending order of priority:

- a) The person's agent pursuant to an advance health care directive
- b) The conservator or guardian of the person having the authority to make health care decisions for the person
- c) The spouse of the person
- d) An individual as defined in Section 297 of the Family Code (a “domestic partner”)
- e) An adult son or daughter of the person
- f) A custodial parent of the person
- g) Any adult brother or sister of the person
- h) Any adult grandchild of the person
- i) An available adult relative with the closest degree of kinship to the person

When there are two or more available persons who may give surrogate informed consent and who are in the same order of priority, if any of those persons objects to have the subject participate in the medical experiment, consent shall not be considered as having been given. Also, consent of a person who is in lower priority cannot supersede the refusal to consent by a person who is a higher priority surrogate.

### **Cognitively-Impaired in Emergency Room Environments**

Surrogate informed consent may be obtained from a surrogate decision maker who is any of the following persons:

- The person's agent pursuant to an advance health care directive
- The conservator or guardian of the person having the authority to make health care decisions for the person

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- The spouse of the person
- An individual defined in [Section 297](#) of the Family Code (a “domestic partner”)
- An adult son or daughter of the person
- A custodial parent of the person
- Any adult brother or sister of the person

When there are two or more available persons described in the above list, refusal to consent by one person shall not be superseded by any other of those persons.

Note that the rules on proxy consent in this statute do not apply to subjects who lack capacity to give informed consent and are involuntarily committed, voluntarily admitted, or admitted on conservator-request to a psychiatric hospital. Investigators should consult the IRB for guidance when the potential subjects are in one of the above categories.