

**TITLE 45  
CODE OF FEDERAL REGULATIONS  
PART 46**

**PROTECTION OF HUMAN SUBJECTS  
Subpart C - Additional DHHS Protections  
Pertaining to Biomedical and Behavioral  
Research Involving Prisoners as Subjects  
Subpart D - Additional DHHS Protections for  
Children Involved as Subjects in Research**



**Q&A by Linda Knowlton, CCRP  
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**Part C**

**§46.301 Applicability.**

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

**§46.302 Purpose.**

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

**§46.303 Definitions.**

As used in this subpart:

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "DHHS" means the Department of Health and Human Services.

(c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass 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.

(d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

**§46.304 Composition of Institutional Review Boards where prisoners are involved.**

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive

of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

**§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.**

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

- (1) the research under review represents one of the categories of research permissible under §46.306(a)(2);
- (2) any possible advantages accruing to the prisoner through his or her 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 his or her 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 nonprisoner volunteers;
  - (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 principal investigator provides to the Board 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 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 his or her parole; and
  - (7) where the Board finds there may be a need for follow-up examination or care of participants 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, and for informing participants of this fact.
- (b) The Board shall carry out such other duties as may be assigned by the Secretary.
- (c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

#### **§46.306 Permitted research involving prisoners.**

- (a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:
- (1) the institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research

under §46.305 of this subpart; and (2) in the judgment of the Secretary the proposed research involves solely the following:

- (A) study 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;
  - (B) study of prisons as institutional structures or of prisoners incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  - (C) 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 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; or
  - (D) 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 has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the **Federal Register**, of the intent to approve such research.
- (b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

#### **Part D**

#### **§46.401 To what do these regulations apply?**

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

#### **§46.402 Definitions.**

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

- (a) "Children" are persons who have not attained the legal age for consent to

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treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

#### **§46.403 IRB duties.**

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

#### **§46.404 Research not involving greater than minimal risk.**

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

#### **§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.**

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) the risk is justified by the

anticipated benefit to the subjects;

(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

#### **§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.**

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) the risk represents a minor increase over minimal risk;

(b) 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;

(c) 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; and

(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

#### **§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.**

DHHS will conduct or fund research

that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 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 children; and

(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, 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 children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

#### **§46.408 Requirements for permission by parents or guardians and for assent by children.**

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some

or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in 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, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, 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. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

#### **§46.409 Wards.**

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) related to their status as wards; or

(2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

## **Self Study Program Guidelines**

If you are interested in writing an article for SoCRA's self study program, please do so by following these guidelines.

Instructions for Contributors:

1. Electronically submit a minimum of four double spaced pages to the editorial staff, SoCRA.
2. Provide a brief and specific title.
3. List at least three objectives and three to ten key words.
4. Obtain written permission to publish any materials that have been published previously.
5. Number any references in the order in which they appear in your article.
6. Determine the number of contact hours you recommend for reading and testing. A minimum of ten questions is required for one contact hour.
7. Provide one correct answer for each question.

The Editorial Staff will review each submission for content, grammar, and punctuation. The Editorial Staff reserves the right to publish, reject, condense, and edit all contributed materials.

# Self Study Questions

## Title 45 Code of Federal Regulations (CFR) Part 46 Protection of Human Subjects (Sections 46.301 – 46.409)

- The regulations in Subpart C are applicable to the biomedical and behavioral research conducted by the Department of Health and Human Services involving \_\_\_\_\_ as subjects.
  - fetuses
  - pregnant women
  - prisoners
  - all of the above
- Any individual involuntarily confined or detained in a penal institution is known as prisoner.
  - true
  - false
- The probability and magnitude of physical or psychological harm that is normally encountered in daily lives of healthy persons is known as \_\_\_\_\_.
  - minimal risk
  - risk
  - high risk
  - all of the above
- The composition of the board where prisoners are involved shall meet the following requirements:
  - at least one board member must be a prisoner
  - a majority of the board shall have no association with the prison involved
  - a and b
  - none of the above
- \_\_\_\_\_ means a child's affirmative agreement to participate in research.
  - Permission
  - Assent
  - Participation
  - None of the above
- The term "parent" can refer to an adoptive parent.
  - true
  - false
- An individual may not serve as an advocate for more than one child.
  - true
  - false
- An individual who is authorized under state or local law to consent on behalf of a child for general medical care is known as a \_\_\_\_\_.
  - guardian
  - parent
  - a and b
  - all of the above
- Which of the following is not an additional duty of the IRB where prisoners are involved:
  - the risks are not commensurate to those of non-prisoner volunteers
  - selection procedures are fair to all prisoners
  - decisions regarding parole are not based on study participation
  - the information is presented in a language which is understandable to the subject population
- \_\_\_\_\_ are persons who have not attained the legal age for consent to treatments or procedures involved in the research.
  - Parents
  - Guardians
  - Children
  - Wards

**This self study qualifies for one hour of SoCRA CE (Continuing Education).**

See answer key on page 20 . Please retain this document for your CE record.

Name \_\_\_\_\_ Date \_\_\_\_\_

trial, actually constitutes, in many instances, assault and battery. There is a pathway toward autonomy that addresses the issue of tort law: capacity. Capacity is a person's functional ability as a decision maker. Table 3 describes standards for determining capacity.

Ensuring understanding of the information on a consent form, relative to the decision that must be made, includes adequate presentation of information, an awareness of the potential participant's attention span, an insight into the issues/problems and therapies presented, and an ability to remember the information in order to make a decision (See *Salgo v. Leland Stanford, Jr. University Board of Trustees – 1975*). To ensure adequate consenting of the research participant and foster self-determination, health care providers obtaining consent should begin to rethink their presentation style and the impact the research has on the patient.

An adequate understanding of the attention span of patients is critical to ensure comprehension. For example, a United States Navy study of submariners, who are considered to be among the Navy's most intelligent personnel, found them to have an attention span of approximately 18 minutes, complete with peaks and valleys. It should be recognized that clinical research professionals are speaking to patients who could be culturally, educationally, or financially disadvantaged in 'physician' language. Therefore, patients often fail to get the message.

Additionally, it is important when communicating with caregivers about a potential participant's decision to enter a clinical trial that the following questions are satisfactorily answered:

- Is the potential subject responsive?
- Can the person discuss his/her decision?

- Does the person have any disorder that would interfere with the capacity for making a decision?

Cognitive and affective capability means answering these questions:

- Can the person relate to the situation based on his/her life experiences?
- Can the person understand the importance of the decision?
- Can the person effectively understand the risk/benefit relationship?
- Does the person display any clinical disease processes associated with altered mental status that would indicate incapacity?

Resolution includes:

- Selecting of an option based on information
- Reaching a conclusion by setting aside uncertainties and participating in decision-making
- Ensuring that the person understands the concept of autonomy.

Obtaining informed consent is obviously a complex process, which clinical research professionals should take significant measures to do correctly, least lawyers, who know relatively little about clinical research, enter the research landscape and start telling the researchers how to do their jobs. Clinical research professionals know what absolutely needs to be done and, to ensure their survival, they must start doing it.

## Self Study Quiz - Answer Key

(See Pg. 10)

### Answers:

1. c. prisoners (Section 46.301 a)
2. a. true (Section 46.303 c)
3. a. minimal risk (Section 46.303 d)
4. c. a and b (Section 46.304 a and b)
5. b. Assent (Section 46.402 b)
6. a. true (Section 46.402 d)
7. b. false (Section 46.409 b)
8. a. guardian (Section 46.402 e)
9. a. the risks are not commensurate to those of non-prisoner volunteers (Section 46.305 [3])
10. c. Children (Section 46.402 a)