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Research Involving Prisoners in Non-Prison Settings: FDA and OHRP Regulations

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Background

Enrolling prisoners in clinical research studies poses an exceptional ethical dilemma. They constitute an especially vulnerable population that has suffered severe abuses in the past. However, they are members of society with just as much right as anyone else to participate in clinical studies. Also, given the challenge of enrolling subjects in many studies, no eligible population should be disregarded. As stated in The Belmont Report, "on the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research… on the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer." Research on prisoners has had long standing ethical issues. The Nazi experiments during World War II resulted in one of the landmark documents on research ethics: The Nuremburg Code (1946). However, as Alan Hornblum's expose' *Acres of Skin* points out, questionable use of prisoners in the United States continued for almost 30 years post-Nuremburg Code. The Belmont Report specifically mentions prisoners in its statement that "some classes of potential subjects (e.g., the institutionalized, mentally infirm, or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Research that is federally funded has statutory requirements for certain vulnerable populations to assure the government that its research funds are not being used unethically. The Department of Health and Human Services (DHHS), through its Office of Human Research Protections (OHRP), set forth its conditions for research involving prisoners in sections 45 CFR 46.301-306 of the federal regulations, also known as "45CFR46, Subpart C," or simply, "Subpart C." OHRP guidance states that "the regulations provide that 'biomedical or behavioral research conducted or supported by HHS shall not involve prisoners as subjects unless the research is specifically authorized within the subpart."[1] Subpart C does not apply only if prisoners are specifically targeted as a population. If a prisoner happens to be a potential subject for a study not targeting prisoners or if an active subject becomes a prisoner while in a study, then Subpart C applies for his or her protection.[2]

A "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."[3] OHRP's FAQ on prisoners furthers this definition by stating, "Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial."[4] Some alternatives to incarceration are also discussed, such as (a) individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing; (b) individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration; or (c) parolees who are detained in a treatment center as a condition of parole.[5] Sometimes it

is not clear whether a person is a prisoner. In such cases, the key words in these definitions (i.e., "confined," "detained," committed") are useful. For example, an individual on parole or out on bail has freedom to move about, so does not meet the definition of "prisoner." A person under house arrest who cannot leave the premises would be considered a prisoner; however, one who can leave the premises would not be considered a prisoner.

The purpose of Subpart C is codified in 45 CFR 46.302, which states, "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." Coercion may take place during the informed consent process or (absent the consent process) through taking advantage of their "ease of access" due to their status as prisoners. There are many kinds of research (such as minimal risk research with waived informed consent) for which Subpart C clearly would not apply based on the stated purpose of Subpart C; however, despite a study design with enough built-in human subject protections for prisoners to meet the spirit and purpose of Subpart C, the letter of the law must still be followed.

How Subpart C Differs from FDA Law and Other OHRP Laws

"Subpart C" is an OHRP law and not a Food & Drug Administration (FDA) law. This means that Subpart C applies only to research that is either federally funded/conducted or if your institution selected one of the optional boxes in Section 4 of your Federal-Wide Assurance (FWA) stating that you apply the Common Rule and all its subparts to all research, regardless of funding source. FDA stated this in the Replies to Inquiries section of their Good Clinical Practices Program by answering the August 28, 2002, question, "please advise on what is required for studies with prisoners":

> "FDA does not have additional requirements that pertain to research involving prisoners; rather, our general requirements for IRB review and informed consent (21 CFR Parts 56 and 50) would apply to such research. However, if the research is conducted or supported by the Department of Health and Human Services (HHS), or conducted in an institution that has assured HHS that it will review all research in accordance with the Common Rule, then the research would be subject to 45 CFR 46, including Subpart C, which provides additional protections pertaining to research involving research with prisoners as subjects. Although those additional practices are not required by FDA, they are a good model to follow."[6]

Subpart C also sets forth differences from the usual OHRP regulations, such as:

- Studies that would meet the OHRP criteria for exemption cannot be exempt if involving prisoners.[7]
- The OHRP defined Waiver of Informed Consent Requirements in Certain Emergency Research is inapplicable to prisoners.[8]
- Even if informed consent is waived or altered based on the usual criteria, Subpart C still requires that subjects be clearly informed in advance that participation in the research will have no effect on their parole, if such notification is relevant.[9]
- The Subpart C definition of "minimal risk" ("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"[10]) alters the Common Rule definition by (a) referring to "physical or psychological harm," rather than "harm or discomfort"; (b) comparing the probability and magnitude of harm in the research to the probability and magnitude of those harms normally encountered in daily life, or in "routine medical, dental, or psychological

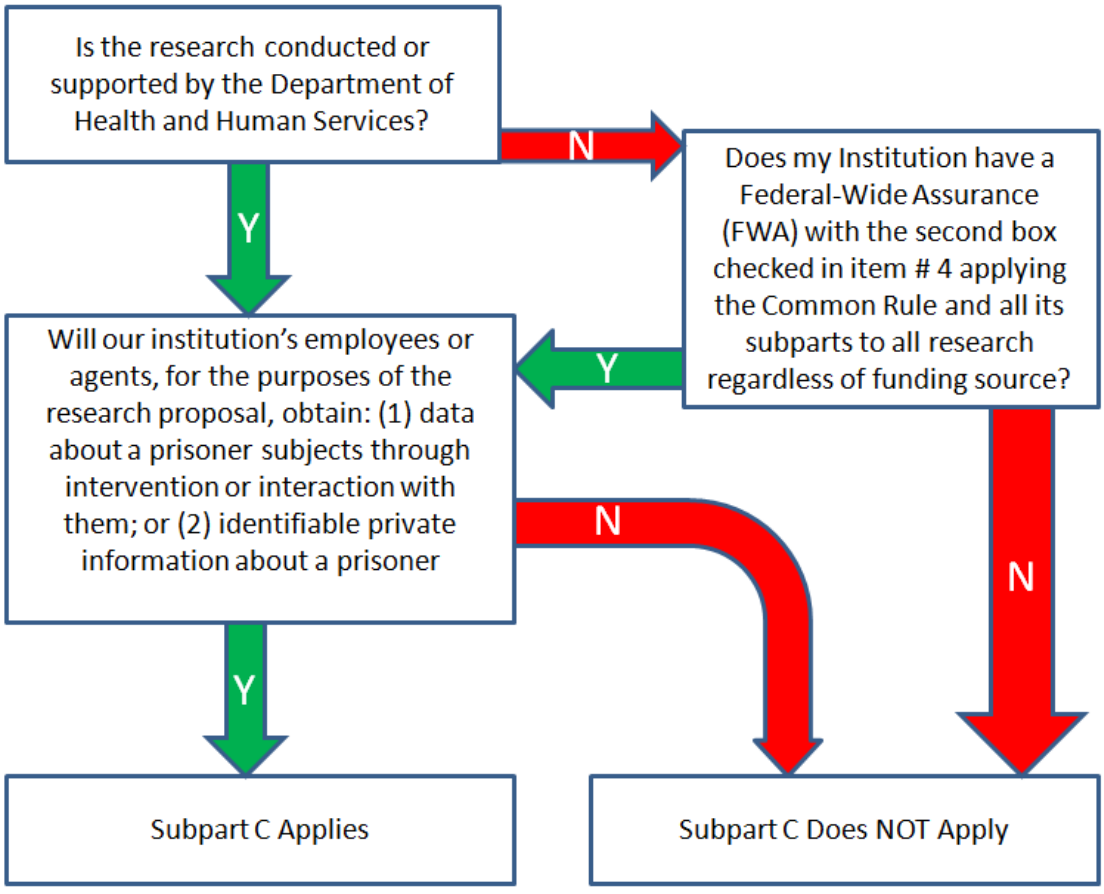
examinations," rather than in daily life or "routine physical or psychological examinations or tests"; and (c) identifies "healthy persons" as the comparison group against which the risks of the research should be measured, rather than leaving the comparison group unspecified, as in subpart A. OHRP interprets the term "healthy persons" in this definition as healthy persons who are not prisoners.

Additionally, even though research involving prisoners can be expedited, OHRP recommends that the convened IRB review research involving prisoners as human subjects.[11]

Conducting a Subpart C Review

The process to determine if a Subpart C review is required — and to conduct one if needed — can be broken down into four basic steps. While you may not plan on targeting prisoners as a population, occasionally one may present himself or herself for your study or an active subject may become a prisoner while in your study. An IRB may conduct a Subpart C review in advance to accommodate these situations if they are likely to happen. If, however, a subject in a study becomes a prisoner while in the study and a Subpart C approval was not done in advance, the investigator must immediately suspend research on that subject (i.e., halt all research interactions or interventions with, and obtaining identifiable private information for research purposes, except to the extent the investigator asserts that it is in the best interests of the subject to remain in the research study) until a Subpart C review is done and the investigator has received authorization from OHRP, if required (See Step 4 below.)[12]

Figure 1. Does Subpart C Apply?



Step #1: Does Subpart C Apply?

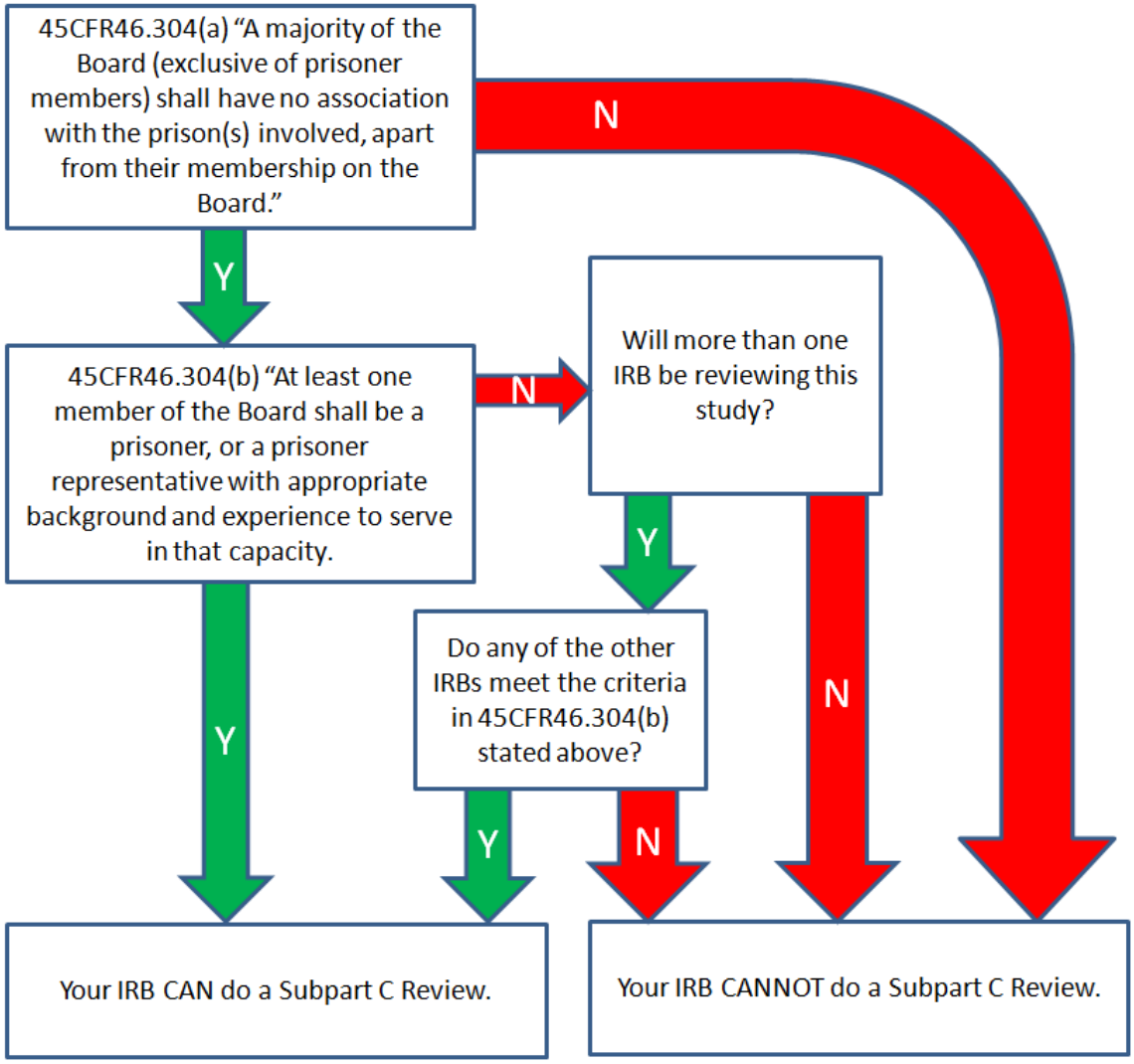
Before you embark on a Subpart C review, first assure yourself that Subpart C even applies. Based on federal regulations and guidance, the decision tree in Figure 1 can be used to make this determination.

OHRP has clear guidance on what it means to be "engaged in research" involving prisoners. Common examples of relevant activities include: (a) seeking the informed consent of prisoners to be subjects in research; (b) using, studying or analyzing, for research purposes, identifiable private information about prisoners, or identifiable specimens obtained from prisoners; and (c) surveying prisoners for a research study."[13]

Step #2: Can my IRB conduct a Subpart C Review?

45 CFR 46.304 requires that the IRB have the appropriate membership to conduct a Subpart C review. In addition to the usual IRB membership requirements, for your IRB to be eligible to conduct a Subpart C review, the decision tree in Figure 2 must be followed.

Figure 2. Can My IRB Do A Subpart C Review?



OHRP guidance clarifies the meaning of "prisoner or prisoner's representative" by stating that "in the absence of choosing someone who is a prisoner or has been a prisoner, the IRB should choose a prisoner representative who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner."[14] OHRP also recommends that IRBs that do not frequently review research involving prisoners register their IRB in one of the following manners:[15]

- Register two IRBs, annotating the name of the IRB with the prisoner representative, for example, "Prisoner Research." This roster would only be invoked and used to determine quorum when the IRB is reviewing a study covered by Subpart C of 45 CFR Part 46. The assurance should list both IRBs; or
- Register one IRB with the prisoner representative and add a "Comment" to the IRB roster identifying the voting member who is the prisoner representative and stipulating that the prisoner representative will only count towards quorum when he or she is in attendance and reviewing studies covered by Subpart C.

Step #3: The Subpart C Review

In addition to the usual criteria required to approve a research study, Subpart C requires that seven additional criteria be met for prisoners to be involved.[16] The first criterion is that the research represent one of the four categories permissible for the prisoner population. The four permissible categories are as follows:

- 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;
- Study 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;
- 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 DHHS 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; or
- 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 DHHS 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.

DHHS allows certain kinds of research under Subpart C that does not fit into the above categories, such as research on chronic diseases, injuries and environmental health. It has therefore created the Epidemiological Waiver for Prisoners (Federal Register June 20, 2003 Pages 36929-36931), which allows for a waiver of this criterion, provided the following conditions are met:

- The sole purpose of the study is (a) to describe the prevalence or incidence of a disease by identifying all cases; or (b) to study potential risk factor associations for a disease.

- The institution certifies that (a) the research presents no more than minimal risk and no more than inconvenience to the prisoner subjects and (b) prisoners are not the particular focus of the research.

Meeting one of the four categories above or the Epidemiological Waiver will suffice for the first of the seven criteria needed to be met to approve research involving prisoners. The remaining six criteria in 45 CFR 46.305(a) are as follows:

- 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;
- The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
- 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 Institutional Review 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;
- The information is presented in language that is understandable to the subject population;
- 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
- 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.

Is it ethical to pay prisoner-subjects for participation, and if so, what should the amount be? Due to the income disparity, compensating prisoners the same amount that would be paid to non-prisoners may be coercive. (It can be argued that the same issue applies to any wealthy vs. poor subjects and yet the stipends remain the same, but prisoners make substantially less than minimum wage or welfare (for example, most Wisconsin inmates fortunate enough to work a 40 hour workweek make $2/week, with the highest-paid earning around $16/week, from which they have to buy basic necessities such as soap, deodorant and toothpaste.[17])) On the other hand, paying prisoners less than non-prisoners may be exploitative. A frequently cited court case on the issue offers suggestions on how to deal with this scenario, none of them entirely satisfactory. The suggested approach is to pay prisoners a rate comparable to compensation for other prisoner tasks. The remaining balance would go to the prisoner's family (or perhaps to the prisoner when the prisoner is released) or to a general educational or recreational fund under the control of prison inmates.[18]

Step #4: OHRP Certification

After your IRB approves the study under Subpart C, 45 CFR 46.305(c) requires your institution to "certify to the Secretary of DHHS, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled." According the OHRP's FAQ on prisoner research, this certification must contain:[19]

- A statement that the IRB reviewed the research under Subpart C and made the seven findings required by 45 CFR 46.305(a)
- A copy of the research protocol
- A copy of any IRB application forms
- Any other information the IRB required the investigator to submit
- The Federal-Wide Assurance number of the institution engaged in the research
- The registration number of the reviewing IRB
- The date of the initial IRB review
- The date of the Subpart C review

Provided OHRP agrees with the certification, it will issue an authorization to use prisoners as subjects. If it does not agree, it will issue a letter stating that the research may not involve prisoners.

In a multicenter study, each institution must provide this certification "unless (a) an institution relied upon the review of an IRB operated by another institution engaged in the research; and (b) that IRB or the other institution certified to OHRP on behalf of both institutions."[20]

It is also important to note that the OHRP FAQ answers the question "Does research involving prisoners not conducted or supported by HHS require certification?" with "No. If research is not DHHS-conducted or -supported, the institution does not need to submit any certification to OHRP, regardless of whether the institution has chosen to extend the applicability of its FWA and Subpart C to all research." By specifically mentioning that "certification" is not required implies only that this Step 4 may be waived, but the other steps of Subpart C must still be followed.[21]

Final Thoughts

To quote the OHRP IRB Guidebook, "Prisoners should neither bear an unfair share of the burden of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible… To the extent that prisoner-subjects are found able to voluntarily consent to participation, and to the extent allowable under applicable regulations, prisoners should be allowed the opportunity to participate in potentially beneficial research." Subpart C offers a detailed methodology when including prisoners in research but it does not apply in all cases, depending on the nature of the research and its funding source. As with any regulation, Subpart C provides a roadmap to these protections (which can be used on an optional basis when not legally required) but the same regulations seem overly burdensome for kinds of research for which it seemingly was not intended (such as when prisoners are not targeted as a population and consent has been waived) because it appears to provide no additional protections for this population. It is important to understand the details of Subpart C, when it applies, and how to apply it so we may have the benefit of prisoner participation in research without jeopardizing their rights or welfare.

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