

National Advisory Council on Drug Abuse Recommended Guidelines for the Administration of Drugs to Human Subjects

I. Preamble

The National Advisory Council on Drug Abuse (NACDA) recognizes the importance of research involving the administration of drugs with abuse potential, and dependence or addiction liability, to human subjects. These drugs may include caffeine, nicotine, alcohol, opiates, cocaine, amphetamine, barbiturates, benzodiazepines and other compounds with known or suspected abuse/dependence liability. This research can produce scientific knowledge that is essential to understanding and addressing problems of drug abuse and addiction, and is particularly important in the development of effective, scientifically based treatment and prevention strategies.

Research involving the administration of drugs must be designed, reviewed, and conducted within the fundamental and broader ethical principles governing all biomedical and behavioral research with human subjects. These principles have been articulated in the Belmont Report, which provides a broad framework for establishing and evaluating specific aspects of ethics in research with human subjects. While a complete reading of the Belmont Report (<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>) is required for a full understanding of these principles and their application in complex ethical issues involved in research on human subjects, the principles can be summarized as follows:

Respect for Persons - Individuals must be given the opportunity to choose what shall or shall not happen to them and their decisions must be informed and protected. Persons with diminished autonomy or capacity are entitled to protection.

Beneficence - Researchers must go beyond the obligation to avoid inflicting harm and maximize the potential benefits of the research to individuals and society.

Justice - Fairness and equality must guide the distribution of the benefits and burdens of research involving human subjects.

The general principles of ethics in human investigation are also addressed in such documents as:

1. the Nuremberg Code of 1947,
2. the Helsinki Declaration of 1964 (most recently revised in 1989),
3. guidelines from professional organizations, such as the American Psychological Association,

4. a number of relevant books including "Ethics and Regulation of Clinical Research," authored by Robert J. Levine (Urban and Schwarzenberg, Baltimore-Munich, Second Edition 1986); and
5. the Code of Federal Regulations (CFR), 45 CFR Part 46, "Protection of Human Subjects".

Investigators conducting NIDA sponsored research outside of the United States and its territories are encouraged to also seek guidance from guidelines/codes/regulations that pertain to that specific research setting.

The Council notes that responsibility for development and implementation of ethical research protocols falls upon more than one individual or group. It rests first with the principal investigator and next with the Institutional Review Board (IRB), as required by the Code of Federal Regulations (CFR), 45 CFR Part 46, "Protection of Human Subjects." IRBs must review and approve all Department of Health and Human Services (HHS) conducted or funded research protocols involving human subjects. The levels of review for projects supported by the Institutes and Centers of the National Institutes of Health are the Scientific Review Groups (SRGs), the National Advisory Councils and Institute staff. Human subject concerns raised by either an SRG or a Council are conveyed to the principal investigator as well as to the applicant's institution. The program staff of the Institute, in consultation with the Office for Extramural Programs (OEP) have the responsibility for resolving human subject concerns before any study involving human subjects can be undertaken. Program staff are responsible for requesting and the OHRP is responsible for negotiating assurances of compliance with institutions that will be engaged in the research and for which no assurances covering the research are in place at the institutions.

However, while these important regulations, principles, and guidelines form an important context for research involving administration of drugs, the NACDA believes there are additional, specific ethical and safety points that must be considered by investigators and IRBs. Thus, these NACDA guidelines focus on the issues that arise in research involving administration of drugs with abuse/dependence liability, and are intended to identify issues to be considered in the development and review of research protocols involving drug administration to human subjects.

II. Purpose of These Guidelines

The guidelines are not intended to supplant the functions of either the IRB or OHRP. They are advisory to applicants, IRBs, IRGs, and others. *They are not codified and do not constitute Federal regulation.* Rather, the guidelines are intended to encourage a sensitive, ethical approach that is also consistent with the best current practices and experience in the field of drug abuse research.

The NACDA also notes that the principal responsibility for approval of a research project involving human subjects rests with the local IRB. Though the SRG, NACDA, and Institute staff have a responsibility to consider human subject issues, it is the local institution and its IRB, which are most aware of the many complex factors affecting the acceptability of proposed procedures. However, it is clear that IRBs have varied in their reviews of drug abuse research, thus, there is a need for uniform guidelines.

Research involving drug administration can raise issues that go beyond protection of

human subjects per se, including the legal or moral concerns often raised by the sensitive behaviors being studied. It is important not to allow these issues to deflect from a proper focus on the dual values of promoting needed scientific research on a critical health problem and on the protection of human subjects. For that reason, specific training and proper expertise of individuals involved in ethical review of projects in this area are especially needed. Thus, the NACDA suggests that local IRBs should obtain outside advice when they do not have sufficient familiarity with drug abuse research issues. Such procedures are consistent with 45 CFR 46.107(f).

III. General Issues

The NACDA recommends consideration of a number of general issues applicable to drug administration research involving human subjects, regardless of the specific population. These issues are:

A. Risk/Benefit

Research with volunteer participants begins with a careful appraisal of all risks and benefits. Considerations include importance and validity of the scientific information to be gained, degree of risk to research participants, and availability of alternative research approaches and information sources. Ultimately, there must be a favorable balance of potential benefit against risk; without this favorable balance, a research protocol cannot be justified.

In assessing the risks and benefits, the IRB should take into account the qualifications and experience of the research team, the appropriateness and adequacy of the research design, and the suitability of any site where the administration of drugs and other interventions occur. Depending on the level of expertise of the research team, a project may not be judged to have an acceptable risk/benefit ratio even if the project has a sound scientific hypothesis and research design. Similarly, the site of the research may influence risk/benefit decisions. The NACDA also notes that the local IRB ultimately is responsible for considering the many complex factors involving the research team's qualifications and experience in conducting similar studies, the suitability of the research site, and local policies affecting the acceptability of proposed procedures.

B. Data Safety Monitoring Board

The NACDA recognizes the importance of a Data Safety Monitoring Board, which is responsible for collecting and analyzing safety-sensitive data during the course of a study to monitor for adverse effects and other trends. Such trends might include a clear indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control. Such data monitoring findings would warrant modification or termination of the trial, or notification of subjects about new information that might affect their willingness to continue in the trial. Information on data safety monitoring is available in the Institutional Review Board Guidebook (1993, Office for Protection from Research Risks), on NIDA's web site at <http://www.nida.nih.gov/Funding/DSMBSOP.html> and in the NIH policy statement at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

C. Informed Consent

The NACDA reiterates the basic principle that the investigator has the primary

responsibility for assuring that the informed consent process gives potential participants all the information they need to make a voluntary and informed decision. IRBs, as well, should assure that the informed consent documents convey all relevant information in language readily understandable by the research participants and/or guardians. Also, the NACDA recommends that the investigator give adequate consideration to the mental and physical conditions and motives of the individuals in terms of their ability to fully understand the context of the informed consent. If there is a question about a potential subject's ability to give informed consent, an independent clinician, ethical consultant, or uninvolved third party with appropriate qualifications should be asked to evaluate this ability if the subject is to be entered or continued in the study. Finally, as discussed in Section B, above, the IRB is responsible that the information in the informed consent is updated with any new findings regarding safety and efficacy of the procedure under investigation.

D. Subject Selection

The NACDA emphasizes the need for care in subject selection so that appropriate participants are recruited to address the research question and to ensure that adequate safeguards are followed to prevent unnecessary risk. The issues relating to subject selection are addressed in more detail in the Section IV.

E. Confidentiality

Investigators should be aware that once drug abuse histories are placed in patient records, such records must be handled with extreme confidentiality. These confidentiality requirements sometimes go beyond those for many other medical or research records. Further, investigators and IRBs should be aware that special Federal requirements might apply to certain drug abuse records used in research. Information about this may be found in the Code of Federal Regulations (CFR) under 42 CFR Part 2, "Confidentiality of Alcohol and Drug Abuse Patient Records."

Investigators also should be aware that the Secretary, HHS, may authorize persons engaged in biomedical, behavioral, clinical, or other research to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of research subjects. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals (42 CFR Part 2a). However, investigators, research participants, and IRBs should be aware that there are no absolute guarantees of confidentiality.

IV. Specific Issues

The NACDA recommends that these important issues be considered in the development and review of research involving the administration of to human subjects.

A. Medical and Psychological Screening and Services

Care should be taken to ensure that study personnel who are administering the drug(s) and who are responsible for the associated care of the subjects have the proper training and experience in administering drugs to humans. Investigators should specify the level of training and experience study personnel will have prior to their direct involvement in drug administration.

Medical and psychological screening procedures must be carried out to ensure that participants chosen for the study will not be harmed by drug administration. To further assure this, appropriate monitoring and medical support services must be available during the study. The amount of medical support necessary will depend on the study protocol (e.g., drug(s) under study, route and rate of drug administration). At a minimum, a nurse or physician available "on call" may be appropriate. This may be amplified to require a nurse to be present with a physician available, or to require a physician to be present, if the demands of the study require it.

Medical and psychological screening procedures may be of particular significance in elderly subjects. Such subjects may be undergoing gradual changes in anatomy and physiology that may alter the effects of drugs.

B. Administration of Drugs to Individuals Who Have Never Used Drugs

It is expected that research involving the administration of drugs of abuse to individuals who have never used drugs prior to study participation would *occur only in the rarest of circumstances and with the strongest justification*. Such research must be justified very strongly within the requirement that (1) the question under study cannot be reasonably or validly answered without their participation and (2) there exists a strongly favorable risk/benefit assessment. It should be remembered that a wide range of potentially abusable drugs might be the focus of drug administration research--from caffeine and nicotine to cocaine and opiates. Depending on the drug, limited investigator-controlled exposure to these drugs may have very different levels of risk for potential participants. Casual drug users may be appropriate research subjects, given that the benefits outweigh the risks of participation.

C. Involvement of Individuals Currently Addicted to Drugs and/or Are Frequent Drug Abusers

Research which requires individuals who are addicted to drugs and/or are frequent drug abusers to be administered drugs warrants special attention. As stated above, investigators should take into consideration current, recent, and past drug use and thoroughly assess the participant's ability to provide informed consent. There are a number of extremely important principles that need to be addressed by anyone considering or evaluating requests to undertake such research. These include the following: a) a serious and concerted effort be made to link these individuals to drug abuse treatment; b) inclusion of medical examination and screening to assure the absence of any medical or mental condition for which further drug exposure would be contraindicated; and c) a thorough assessment of the risks entailed if participants are to be exposed to higher doses, rate of administration, and/or new route of administration than they would normally encounter by their own choice in their usual circumstance.

If the subject has participated in prior drug intervention trials, a list of previous dosing regimens, (i.e. drug, dosage, frequency, duration), should be included in the evaluation record. Prior drug failures should be indicated. If the patient currently is taking (or has been prescribed) medications to prevent or reduce addiction, similar information should be evaluated. Extreme care must be exercised when admitting any patient in a trial when the subject is taking any concomitant medication. Possible drug interactions should be evaluated thoroughly before admitting the

patient in the trial. Concern regarding drug interactions between the test drug and concomitant medications (prescribed for the subject for preexisting conditions) is sufficient in some cases to exclude subjects from a study.

D. Administration of Drugs to Incarcerated Individuals

In accordance with the Code of Federal Regulations (CFR) 45 CFR Part 46 Subpart C, additional protections must be given to research involving prisoners as subjects. Such consideration is given because prisoners may be under constraints to full voluntary participation in a research project because of their incarceration and/or the conditions of their legal supervision.

E. Administration of Drugs to Individuals with Mental Disorders

In addition to the basic protections offered in the Code of Federal Regulations, additional protection must be given to research involving persons with mental disorders that may affect decision making capacity. Persons with such disorders may have impaired capacity to give voluntary consent that must be considered. Investigators are encouraged to review the recommendations of the National Bioethics Advisory Commission, "Research Involving Persons with Mental Disorders That May Affect Decision Making Capacity" (December 1998). Administration of drugs that might exacerbate existing mental conditions either acutely or chronically must have a compelling rationale.

F. Drug Doses and Routes of Administration

To minimize the risk, participants should be exposed to the least amount of drug necessary to achieve the purpose of the study. Sometimes it may be necessary for participants to be administered new drugs and/or doses of drugs greater than that they would normally consume by their own choice in their usual circumstance, or to be exposed to a new route of administration. Under those circumstances, the rationale for exposure to new drugs, to higher doses, or to new routes of administration should be clear and compelling.

G. Prior and Current Drug Treatment Status

Another factor that must be taken into consideration in any decision regarding administration of drugs of abuse to human subjects is the subject's current and prior drug treatment experience. With regard to subjects currently in treatment, administration of drugs of abuse as part of an experimental study rarely is appropriate and should only be done under the most structured circumstances. This is because there is great risk of impeding a subject's efforts at rehabilitation.

In general, in-treatment or treatment-seeking individuals should not be given drugs of abuse. However, there can be circumstances in which such research is appropriate. In-treatment or treatment-seeking individuals who have an addiction history may be uniquely appropriate for some types of research. In these cases *investigators have a special burden to establish a compelling rationale for the inclusion of these participants*. Priority always must be given to what is in the best interest of the participant/patient. Participants should not be recruited simply for the convenience of the investigator. **Any situation where drug administration could potentially interfere with the treatment process or motivation of the patients almost certainly will be contraindicated.**

Investigators also have an additional burden for ensuring proper participation in the informed consent process. Among current and past drug users, special issues arise regarding their interest in, and level of commitment to, abstinence. Treatment providers should be consulted with consent of the subjects prior to use of such subjects.

H. Prior and Current Treatment Experience

If the subject has participated in prior drug intervention trials, a list of previous dosing regimens, (i.e. drug, dosage, frequency, duration), should be prepared. Prior drug failures should be indicated. If the patient is on current therapy for possible efficacy against a substance of abuse, similar information should be obtained. Care must be exercised when admitting any patient in a trial when the subject is taking any concomitant medication. Possible drug interactions should be evaluated thoroughly before admitting the patient in the trial.

I. Women With Childbearing Potential

Women of childbearing potential should not be automatically excluded from participation in clinical research. The NIH policy is that women must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling reason shows that inclusion is inappropriate.

J. Pregnant Women

Risk/benefit considerations virtually always would preclude administration of drugs to pregnant women as this may endanger the fetus. One notable exception would be in the treatment of pregnant, substance dependent subjects. Therefore, it is the responsibility of the investigator to have a very compelling rationale for such a study; and to take adequate precautions, throughout the study, to prevent inappropriate administration of drugs to women who are, or may be, pregnant. Pregnancy always must be assessed using an acceptable pregnancy test. While menstrual and contraceptive history may be useful, the assessment of pregnancy status should not be made solely by self-reported information. As with all research, investigators and IRBs must adhere to the additional requirements pertaining to research involving fetuses, pregnant women, and human in vitro fertilization as contained in HHS Regulations for the Protection of Human Subjects, 45 CFR Part 46, Subpart B.

K. Special Considerations Across the Lifespan

If the hypothesis being tested requires the involvement of individuals under age 18 and the risk/benefit assessment is favorable, the investigator must: (1) obtain the individual's consent and/or assent to participate in the study; (2) obtain permission from the parent(s) or guardian for the individual to participate in the study, as appropriate; and (3) comply with any applicable local laws governing such research. As with all research, investigators and IRBs must adhere to the additional requirements for the protection of children involved as subjects in research, as contained in HHS Regulations for Protection of Human Subjects, 45 CFR Part 46, Subpart D.

As stated in Section IV, Part A, elderly subjects also constitute a vulnerable population. Such subjects must be given special considerations because they may be undergoing gradual changes in anatomy and physiology that may alter or be altered

by the metabolism and short and long-term effects of drugs.

L. Study Personnel Training and Experience

Care should be taken to ensure that study personnel who are administering the drug(s) and who are responsible for the associated care of the subjects have the proper training and experience in administering drugs to humans. Investigators should specify the level of training and experience study personnel must have prior to their direct involvement in drug administration.

M. Infection Risk Reduction Counseling and Testing

Persons that use drugs are often at special risk for contracting and transmitting HIV, tuberculosis (TB), hepatitis, syphilis and other infectious diseases. Infection risk reduction interventions have been demonstrated to effectively reduce these behaviors. NIDA has established a policy (NIH Guide for Grants and Contracts, June 9, 1995) that strongly encourages NIDA-funded researchers to offer HIV education and counseling and infection testing available to research subjects.

N. Safety of Research Participants Outside of the Research Site

A concern is the possibility that individuals who have been administered drugs in a study may still be under the effects of those drugs and, upon leaving the laboratory, drive or engage in behavior that may be harmful to themselves or others. The consent form and research protocol should address the estimated period of time that the research participant likely will have to stay at the research facility. Participants must be kept under observation for that period and when dismissed from the laboratory, participants should be informed of the potential performance impairments to be expected during this period. Investigators also should determine, depending on the nature of the study and the subject, the likelihood of any delayed reaction from participation in the study. Discharge personnel should have the necessary training and experience to determine whether the subject is impaired. If it is determined that the subject is impaired, provisions should be made to provide the appropriate intervention.

O. Referral to Treatment

Investigators should be knowledgeable about available drug abuse treatment options and, where medically indicated, offer research participants referral to treatment before, during, and at the conclusion of study participation. Investigators who identify co-morbid or coincident diseases in study participants should provide or refer them to appropriate medical care.

P. Incomplete Disclosure

On relatively rare occasions, an element of deception or incomplete disclosure of information about the research methods or goals may be justified in drug abuse as well as other research; for example, when researching expectancy and placebo effects. Any such withholding which results in the exclusion or alteration of some or all of the elements of informed consent in 45 CFR Section 46.116 must be approved by the IRB in accordance with the waiver requirements of 45 CFR Section 46.116(c). At the conclusion of participation in the research protocol, research participants should have a general and study specific debriefing. In addition, participants should have the opportunity to be informed of study results and their

significance upon completion of the study analysis.

The consent form should clearly indicate that they might receive drugs, the types of drugs, and information on the amount they may receive. **Information about risks must never be withheld** for the purpose of eliciting the cooperation of volunteer participants. Truthful answers must always be given to direct questions about research. (See also page 6 of the Belmont Report.)

Q. Payment for Participation in Research

Payment to research participants for their time and inconvenience is an acceptable practice in drug abuse as well as other biomedical research. The payment should not be exploitive or coercive in the sense of unduly tempting individuals to participate. In this regard, alternatives to cash payments should be considered (e.g., vouchers for food, movies, clothing, etc.). When cash payments are considered important and appropriate, the payment could be made in installments or to a third party.

Conclusion

These principles represent a brief summary of basic issues relating to research involving the administration of drugs to human subjects. It should be recognized that there are benefits in addition to risks to individuals who participate in research. Such benefits may include medical and psychological evaluation, HIV counseling and testing, and referral to drug abuse treatment.

Further information on human subject research may be obtained from the Office for Human Research Protection and from the National Institute on Drug Abuse at the following locations.

Office for Human Research Protection
6100 Executive Boulevard, Suite 3B01
Rockville, MD 20892-7507
(301) 496-7005

National Institutes of Health
Office of Human Subjects Research
Office of Intramural Research
9000 Rockville Pike
Building 10, Room 1C116 (MSC 1154)
Bethesda, MD 20892-1154
(301) 402-3444

National Institute on Drug Abuse
Office of Science Policy and Communications
National Institute on Drug Abuse
6001 Executive Boulevard,
Bethesda, MD 20892-9591
(301) 442-6071

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