I. ALCOHOL AND DRUG RESEARCH

INTRODUCTION

Alcohol and drug research focuses on use, abuse, and dependence on abuse-liable substances, and may or may not involve the administration of an abusable substance. It may seek to investigate physiological responses to alcohol or drugs, or may be aimed at the treatment of alcohol or drug abuse. Treatment protocols may be behavioral or biomedical, including the administration of medications.

DEFINITIONS

Abuse-liable: Pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both illicit drugs (e.g., heroin) and licit drugs (e.g., methamphetamines).

IRB CONSIDERATIONS

Research on alcohol or drug use raises special concerns for IRBs because the research often involves the administration of abuse-liable substances. Further, subjects' capacity to provide informed consent is often compromised. Institutionalization may also have an impact on the prospective subject's ability to choose freely to participate in research.

Other issues IRBs need to consider are the selection of subjects and confidentiality. With respect to confidentiality, federal, state, and local laws regarding criminal behavior must be considered, because legal requirements may impinge on the ability of the researcher to guarantee confidentiality. Finally, researchers may face ethical problems with the study design, such as the morality of giving alcohol to alcoholics, or the problems associated with studies that include placebo arms.

The National Advisory Council on Alcohol Abuse and Alcoholism (the Council) has issued guidelines entitled Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation (1989). Many of the recommendations apply equally well to studies involving abuse-liable drugs. The Council's recommendations contain a series of questions and answers about research involving alcohol administration to human subjects, and should be consulted by IRBs reviewing protocols involving alcohol- or drug-related research.

Risk/Benefit. A number of issues raised by alcohol and drug research focus on considerations of risk and benefit. Where alcohol or drugs will be administered to subjects, IRBs should consider, for example, whether the subjects are drug or alcohol abusers, and whether participation of the proposed populations is likely to expose the subjects to harm [see the Recommended Council Guidelines (1989), pp. 5-6]. Investigators must adequately assess the potential for toxicity, and make provisions for clinical care of subjects where it will likely be needed. Further, the need for access to medical backup services (i.e., the presence of a nurse or physician during conduct of the research, or the availability of a physician "on call") should be considered.

Other risks presented by some drug or alcohol research are those inherent in self-administration of abuse-liable substances. IRBs should consider such risks, including the possibility that subjects may self-administer an increasing amount of the drug to levels higher than those to which they are accustomed, and the possible harms that might result.

Where the study has a placebo arm, investigators need to consider the various effects the use of placebos might have and provide mechanisms for dealing with them so that subjects are adequately protected. For example, in a study in
which subjects are told that the investigational agent blocks the effect of an abuse-liable drug, a subject, believing
herself not to be in the placebo arm, might self-administer sufficiently large doses of the drug to fatally overdose.
Investigators should be prepared to address this issue (e.g., through informed consent, monitoring, use of an in-
patient subject population, or other means).

Adequate provisions must be made to eliminate the risk of drug or alcohol impairment before the subject leaves the
research site.

The Council Guidelines describe investigators' obligations to facilitate the entry of alcoholics who are current, active
drinkers into treatment programs [p. 6]. The Guidelines go on to point out that where potential subjects "have
completed the initial phase of treatment and progressed into rehabilitation or recovery," their involvement in
research in which alcohol will be administered requires "extremely strong scientific justification and risk/benefit
assessment" [p. 6]. Further, Council policy holds that "it is considered inappropriate to administer alcohol to any
recovering alcoholic who is abstinent and living a sober life in the community" [p. 6].

In addition to the risk/benefit questions discussed here, the Council Guidelines also consider such issues as the age
of subjects, the involvement of alcohol-naïve subjects, deception or incomplete disclosure, medical and
psychological evaluation of subjects prior to participation, and follow-up of subjects.

Incentives for Participation. IRBs should consider whether any remuneration offered to subjects for their
participation is appropriate. Any remuneration (e.g., money, food, lodging, or medical care) should be
commensurate with the burden of participation, and should not be such that it constitutes an undue inducement or is
coercive.

The possible involvement of drug or alcohol abusers in drug and alcohol research has led some investigators not to
offer any remuneration to their subjects for fear of unfairly inducing their participation. Many potential participants
are unemployed or otherwise economically disadvantaged, so that concern over this issue is appropriate.
Nonetheless, to assume that any remuneration given to alcohol and drug abusing constitutes an undue influence is
also unfair. IRBs should consider this issue carefully.

Informed Consent. In drug and alcohol research, concerns about the consent process focus on determining the
competence of subjects to consent to the research and effectively communicating the information necessary to obtain
informed consent. With respect to competence, IRBs should ensure that competence is assessed rather than assumed.
Because there are no generally accepted standards for determining competence to consent to research, the IRB plays
an important role in assessing the researcher's proposed procedures. IRBs should take an active part in helping
researchers formulate appropriate criteria and procedures, taking into consideration the degree of risk presented. The
same or similar considerations as those discussed Guidebook Chapter 6, Section D, "Cognitively Impaired," would
apply, noting, however, that the capacity to consent to research may fluctuate, depending on the subject's state of
inebriation.

The Council recommendations on competency to consent state that:

- due consideration should be given to the cognitive, physiologic and motivational states of the
  individuals in terms of their ability to fully understand the context of the informed consent.
  Individuals who are severely intoxicated or in a confusional withdrawal state are unable to give
  true informed consent. Alternatively, a blood alcohol concentration (BAC) of zero for the potential
  subject may not be a required prerequisite, depending upon cognitive capabilities of the individual
  at that time. If there is a question of a potential subject's ability to give meaningful informed
  consent, an independent clinician, ethical consultant, or uninvolved third party with appropriate
  qualifications may be asked to evaluate this ability [p. 4].

In drug research, the lack of physical measures for levels of drugs means that investigators must rely (as must
alcohol researchers, in many instances) on clinical judgments based on other indications of mental competence (e.g.,
through evaluating the prospective subject's ability to converse or observing his or her motor skills).
The consent document must use language that is understandable to the subject population, including ethnic sensitivities. Further, the Council states its belief that "it is appropriate that every informed consent form should indicate that the drug, alcohol, is a toxin and a reinforcing agent which may cause changes in behavior, including repetitive or excessive consumption. Such a statement would appropriately acknowledge that alcohol is not an innocuous substance, and that everyone who drinks alcohol is at some risk" [p.4].

Investigators should be aware of federal, state, and local laws regarding criminal behavior, and any possible reporting requirements, whether they relate to criminal activity or other issues, such as HIV serostatus (see Guidebook Chapter 5, Section F, "AIDS/HIV-Related Research"). They should give the IRB evidence that they have considered these requirements and provide a means of dealing with them. The IRB should seek legal advice if necessary. The consent document should explain any limits on the investigator's ability to provide confidentiality of the data, including any required reporting to law enforcement or health authorities. [See also discussion of certificates of confidentiality below and in Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

**Subject Selection.** The question of subject selection also requires IRB attention. Drug- or alcohol-dependent individuals should not be taken advantage of. As the Council states, researchers must "avoid using subjects merely because of their easy availability, low social or economic status, or limited capacity to understand the nature of the research." Furthermore, IRBs should ensure that the proposed subject population is appropriate in terms of age, sex, familial or genetic background, prior alcohol use, other drug use, and general medical and psychological condition, including, if appropriate, alcoholism recovery status. IRBs should consult the Council's recommendations, which describe these issues in greater detail.

IRBs must take into consideration the fact that the subject population of alcohol abusers and users of illicit drugs might include a significant number of adolescents. The protocol must address this issue. If subjects who are not adults participate, the additional protections for of 45 CFR 46 Subpart D apply. [See Guidebook Chapter 6, Section C, "Children and Minors."]

**Privacy and Confidentiality.** Records indicating alcohol abuse or illicit drug use are of an obviously sensitive nature, and must be provided appropriate confidentiality. Methods for assuring adequate protection of the privacy of subjects and the confidentiality of the information gathered about them (including the fact of participation in a drug or alcohol treatment program) should also be described by the investigator. Individually identifiable information that is "sensitive" should be safeguarded; requests for the release of such information to others, for research or auditing, should be allowed only when continued confidentiality is guaranteed.

To protect data against compelled disclosure, investigators may request a certificate of confidentiality from an appropriate federal official [42 CFR 2 and 2A]. For example, the directors of the National Institute of Mental Health, the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse are authorized to grant such protection for research on mental disorders or the use and effects of alcohol and other psychoactive drugs.

IRBs and investigators should note, however, that certificates of confidentiality protect research data from compelled disclosure; they do not cover voluntary disclosures (e.g., reporting of communicable diseases or suspected child abuse). The consent document should not, therefore, promise that "no information will ever be released," but should clearly spell out what can and cannot be released.

For information on certificates of confidentiality, contact:

**National Institute on Alcohol Abuse and Alcoholism**

Dr. Fulton Caldwell  
National Institute on Alcohol Abuse and Alcoholism  
16C-05 Parklawn Building  
5600 Fishers Lane  
Rockville, MD 20850  
Tel: (301) 443-0796
National Institute on Drug Abuse

Ms. Jacqueline R. Porter
National Institute on Drug Abuse
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Cmdr. Lura S. Oravec
National Institute on Drug Abuse
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Rockville, MD 20850
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National Institute of Mental Health

Dr. Anthony Pollitt
National Institute of Mental Health
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Other health research

Mr. John P. Fanning
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For further discussion of certificates of confidentiality, see Guidebook Chapter 3, Section D, "Privacy and Confidentiality."

IRB Membership. IRBs that regularly review research involving vulnerable subjects are required by DHHS and FDA regulations to consider including among their members one or more individuals who are knowledgeable about and experienced in working with those subjects [45 CFR 46.107; 21 CFR 56.107]. In addition, the IRB must be sure that additional safeguards are in place to protect the rights and welfare of these subjects [45 CFR 46.111(b); 21 CFR 56.111(b)].

For Further Information. Investigators and IRB members wishing to discuss drug research involving human subjects should contact:

Cmdr. Lura S. Oravec
National Institute on Drug Abuse
5600 Fishers Lane, Room 10A-55
Rockville, MD 20850
Tel: (301) 443-6071
POINTS TO CONSIDER

1. Does the IRB's membership include sufficient expertise for reviewing the protocol?

2. Will the subject's drug or alcohol dependency create a deficient mental status which will preclude the subject's continuing ability to consent to participation in research? Will prospective subjects be in either a state of intoxication or withdrawal when approached to consent to participation? What mechanisms are proposed for evaluating subjects' competence to consent? Are they adequate?

3. Have additional safeguards been implemented to minimize risks (e.g., pregnancy tests or procedures for ensuring that subjects cannot leave the research site while intoxicated)?

4. Are there federal, state, or local laws regarding criminal behavior or reporting requirements that must be considered? How will they be dealt with? Will prospective subjects be informed of any reporting requirements?

5. Have the investigators provided for maintaining subjects' privacy and confidentiality? Should the investigators obtain a certificate of confidentiality to protect against compelled disclosure of their data?

6. Are adolescents potential participants? Have the additional requirements of 45 CFR 46 Subpart D been met? [See Guidebook Chapter 6, Section C, "Children and Minors."]

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the protection of human subjects

Federal Policy §___.116 [Informed consent]

21 CFR 50.20 and 50.25 [FDA: Informed consent]

45 CFR 46 Subpart D [DHHS: Additional protections for children involved as subjects in research]

Federal, state, and local laws governing disclosure or reporting of criminal behavior (e.g., use of illicit drugs)

Federal, state, and local laws governing confidentiality of information