National Institute on Alcohol Abuse and Alcoholism

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In this Section

Administering Alcohol in Human Studies

The National Advisory Council on Alcohol Abuse and Alcoholism advises the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Secretary of the Department of Health and Human Services (DHHS) on program and policy matters in the field of alcohol abuse and alcoholism. The recommended Council Guidelines represent National Advisory Council recommendations for consideration by research grant applicants, Institutional Review Boards, Initial Review Groups, and others in the alcohol research field. The recommended Council Guidelines are not official Federal NIAAA or DHHS regulation or policy.

Table of Contents

Section

I. PREAMBLE

Research involving the administration of alcohol to human subjects is a critical experimental approach that is essential to address fundamental questions on the etiology, treatment and prevention of alcohol abuse and alcoholism. However, ethical principles exist that must be adhered to in the conduct of such research, and other issues warrant consideration. The National Advisory Council on Alcohol Abuse and Alcoholism (NACAA) has engaged in updating the revised guidelines from June, 1989 to ensure that full and continuing attention will be paid to the fundamental ethical principles that govern all research involving human subjects.

Fundamental ethical principles for research involving human subjects include the concepts of respect for persons, beneficence, and justice. These principles have been well summarized in a report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research, titled "*Ethical Principles and Guidelines for the Protection of Human Subjects of Research*" (The Belmont Report), (OPRR Reports, NIH, DHHS, April 1979, FR Doc. 79-12065). The general principles of ethics in human investigation are also addressed in such documents as the Nuremberg Code of 1946, the Helsinki Declaration of 1964 (revised in 1975, 1983, 1989, 1996, and 2000), in guidelines from professional organizations such as the American Psychological Association, and in a number of relevant books including Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary by Ezekiel Emanuel, 2004). As a comprehensive presentation of the fundamental ethical principles of research is beyond the scope of these guidelines, a link to the Belmont Report is provided. It can be located at the following Web site: http://ohsr.od.nih.gov/guidelines/belmont.html. In addition, an NIH booklet containing guidelines on conducting human subjects research can be found at http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf. This booklet is in its 5th printing (2004) and represents current NIH policies.

Important aspects of research practice are derived from these ethical principles. Respect for the person requires meaningful, informed, and voluntary consent. Beneficence requires that researchers shall refrain from doing harm and, wherever possible, they should promote the well-being of the research subjects and other individuals with a similar disease, or society as a whole. The selection of research subjects must apply principles of justice.

Responsibility for development and implementation of ethical research protocols falls upon more than one individual or entity. Responsibility 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"). An IRB must review all HHS conducted or funded research protocols involving human subjects. The subsequent levels of review (for projects supported by the Institutes and Centers of the National Institutes of Health) are, in turn, the Scientific Review Groups (SRGs) and the National Advisory Council. Though these bodies most often are not provided the same extensive detail on human subject protocols as provided to IRBs, they are required to call attention to any issues for which there may be ethical concerns. Human subject concerns raised by either the SRG or 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 Extramural Program Policy Officer in the Office of Extramural Research of the National Institutes of Health, have the responsibility for resolving human subject concerns raised by the Council, before any study involving human subjects can be undertaken.

The regulations and offices described above provide a very necessary foundation and context for any research involving the administration of alcohol to human subjects. In addition to these sources, ethical and safety issues that are specific to alcohol administration should be considered by investigators planning alcohol administration protocols.

II. GENERAL ISSUES

Risk/Benefit

Research with volunteer human subjects must take into careful consideration potential risks and benefits, to the subject as an individual, to social groups, and to society at large. A reasonable balance of risk versus benefit must be achieved in order to justify ethically a research protocol.

Considerations include the quality of the proposed protocol, the value of the information to be gained, the degree and type of risk to subjects, the availability of alternative means of acquiring the same type of information, the qualifications of the research team involved, and the suitability of the site(s) chosen for the human subjects research. 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 any proposed procedures.

Informed Consent

The investigator has the responsibility of ensuring that research subjects are informed of both short and long term risks and that they have all relevant information required for making an informed decision. The IRB should ensure that the informed consent documents convey all information in language readily understandable by the research subject or guardian. The individual assigned responsibility for obtaining informed consent must ensure that that the research subject has the capacity to understand, and does understand, the information provided in the consent form. The consent form must document that consent was voluntary and unequivocal. Informed consent forms should address potential risks associated with exposure to alcohol in that particular protocol.

Due consideration should be given to the cognitive, physiologic, and motivational states of the individuals in terms of their ability to fully understand the content of the informed consent. The ability to provide informed consent is a capacity that may be affected by permanent or transient medical, emotional, or legal constraints. When 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 at the time that informed consent is obtained. If the subject cannot provide informed consent, it must be obtained from a representative of the research subject; however, assent from the subject is necessary.

Subject Selection and Evaluation

The need for care in subject selection is emphasized so that appropriate subjects are utilized to address the research question and so that adequate safeguards are followed to prevent unnecessary risk to subjects. It is important to avoid using subjects merely because of their easy availability, low social or economic status, or limited capacity to understand the nature of the research. Significant considerations include the need to consider the subject's age, sex, familial or genetic background, prior alcohol use, other drug use, and general medical and psychological condition, including, if appropriate, alcoholism recovery status. The duration of responsibility for these considerations continues until termination of subject participation. The issues relating to subject selection are addressed in more detail in the following section on specific issues.

Subjects should be screened prior to participation for both scientific and safety reasons. The level of this screening will depend on the context, the nature of the study, and the risks involved in the study. At a minimum, a self-reported medical history should be obtained, including a list of past and current serious medical conditions and any current medications. Decisions about inclusion or exclusion should be made in consultation with a qualified health professional. Psychological well being should also be assessed for both safety and scientific reasons.

Confidentiality

Investigators should be aware that once alcohol histories are placed in medical charts, such charts must be handled with the increased confidentiality afforded other alcohol records. Special federal requirements that apply to certain alcohol records used in research are addressed in the Code of Federal Regulations (CFR) under 42 CFR Part 2, "Confidentiality of Alcohol and Drug Abuse Patient Records."

The Health Information Portability and Accountability Act (HIPAA) is not addressed in this document but relevant guidance can be found at http://privacyruleandresearch.nih.gov/clin_research.rtf.

III. STATUS OF ALCOHOL USE

Protections for Alcohol-Naïve Individuals

In general, alcohol should not be administered to alcohol-naïve subjects. The first exposure to alcohol is a necessary condition for any subsequent alcohol related problems, and currently, researchers do not know which alcohol-naïve individuals may be at risk for subsequently developing alcohol-related problems. Therefore, the first exposure to alcohol has an unknown level of risk.

Inclusion of Populations at Risk for Alcohol Dependence

Individuals with certain familial and/or genetic backgrounds are at higher risk for the development of alcohol dependence, including individuals with a family history of alcohol dependence. Other individuals at risk include those with a history of adverse responses to alcohol, and those with any other empirically determined risk related to alcohol exposure or the proposed method of alcohol administration. Thus, special consideration needs to be given to the risk/benefit assessment before exposing any such subject to alcohol, and even more so when either dosage levels exceed the normal drinking practice of the subject.

Inclusion of Alcohol Dependent Populations

Experimentation that requires individuals who are alcohol-dependent (alcoholic) to be exposed to alcohol warrants special attention. Issues that are essential to address include: 1) medical examination and screening to assure the absence of any medical or mental condition for which further alcohol exposure at the dose contemplated would be contraindicated; 2) assessment of current treatment-seeking status, duration of abstinence within the treatment regimen and the risks entailed through exposure to alcohol.

It is also noted that a serious and concerted effort should be made to link alcohol dependent research subjects who are not in treatment with treatment services. This linkage should be active in bringing together the subject with alcoholism treatment personnel, and not passive as in only providing names of treatment programs and phone numbers to the research subject.

Alcohol-Dependent Subjects and Stages of Treatment

Preferably, alcohol administration experiments should be conducted in individuals who are not seeking treatment; however, efforts to encourage such individuals to enter treatment should be made, as noted in the paragraph above.

In some circumstances alcohol exposure or alcohol cue exposure research may be appropriate in individuals who are seeking or receiving abstinence-oriented treatment. A strong scientific justification for why the question under study cannot be answered reasonably or validly without the subject's participation and a strongly favorable risk/benefit assessment are both necessary. For individuals in abstinence oriented treatment, the research staff and the treatment personnel, with the subject's permission, should consider the potential for untoward effects on the treatment/recovery process. Treatment should be continued after conclusion of research participation for a sufficient period to ensure continued recovery.

Duration of Abstinence

A special circumstance involves the risk of eliciting a withdrawal reaction in actively drinking alcohol dependent individuals who enter a research protocol requiring a period of abstinence. With strong justification, short term abstinence prior to alcohol administration may be instituted for the purposes of the study, with appropriate safeguards (e.g., selection of subjects who are not at risk for significant withdrawal symptoms, provision of medical supervision). This period of abstinence should be kept relatively brief (e.g., consistent with periods of abstinence normally experienced by the participant or a few days).

For subjects in the early phase of treatment who may have achieved a short-term period of abstinence, the consent form should advise the subject that the administration of alcohol under experimental conditions to individuals who have alcohol problems might cause relapse to heavy drinking. Scientific evidence supporting this position is incomplete; however, this conservative approach will provide subjects with information about this potential risk. Again, substantial efforts should be made to help reestablish abstinence following the experiment.

As in the 1989 Guidelines, subjects who have achieved a sustained period of abstinence while living in the community should not be included as subjects in research involving alcohol administration. Although the risk of provoking relapse through experimental administration of alcohol has not been studied in research, the attainment of long-term abstinence by these individuals is a recognized achievement that should not be subjected to any risk of a return to drinking by administration of alcohol.

IV. STAGE OF LIFE CONSIDERATIONS

Younger Populations

Many individuals under the age of 21 consume alcohol, often in patterns that are at hazardous or binge levels and that warrant an alcohol use disorder diagnosis. Recent epidemiological evidence indicates that the prevalence of alcohol use disorders in the United States is at its highest during late adolescence. Nonetheless, the administration of alcohol to underage youth raises a number of concerns. Beyond the legal issues specific to the jurisdiction where the research takes place are areas of specific harm that may be particularly salient with underage populations. These include: (1) implicit legitimization (i.e., sanctioning) of a behavior that is both illegal outside of the research setting and potentially harmful; (2) the increasing number of findings suggesting that adolescent brains may be particularly vulnerable to alcohol-related injuries; and (3) yet-to-be-established dose/response parameters relating to various aspects of acute and long-term harm from alcohol in this population.

Weighing against these risks are the potential benefits for participants and society at large, and these may be considerable. For example, given that adolescent and young adult drinking is an important health issue, better understanding of alcohol effects on these younger drinkers can inform prevention and treatment efforts. Moreover, the experience of younger subjects in the laboratory may be different from their experiences when consuming alcohol in their customary ways and contexts, and could provide potentially health-promoting information to the participant about the effect of alcohol as a drug. Thus, there may be situations in which the risk/benefit ratio is favorable. The risks to participants may be minimized by using low doses.

In the situation where the risk/benefit ratio is deemed favorable and administration of alcohol is legal, use of subjects below the age of legal majority requires written consent of parents or guardians as well as assent of the subject.*

The legal issues concerning underage consumption, to the extent possible, should be viewed as separate from the ethical issues concerning harm to minors while recognizing that the two are not totally independent (e.g., implicit sanctioning of an illegal behavior).

Pregnancy

The possibility of pregnancy should always be assessed by hormonal assay of urine immediately prior to each alcohol administration, and women who are pregnant excluded from participation. Research on alcohol and pregnancy has continued to define the range of prenatal alcohol-derived adverse birth outcomes and to uncover cognitive and behavioral problems that may arise at alcohol exposure levels below those associated with the fetal alcohol syndrome (FAS). Alcohol teratogenesis is now recognized to fall along a continuum and the term fetal alcohol spectrum disorders (FASD) has been adopted to encompass the full range of prenatal alcohol-derived injury. Unless and until a safe threshold is established, pregnant women should not be included in alcohol administration studies.

The Elderly

Public concern about excessive drinking in the elderly is increasing as life expectancy increases. Moreover, certain disorders include illnesses that occur with greater frequency in the elderly, and should be included in the consideration of potential adverse medical consequences of alcohol administration.

* Please see Glossary.

V. OTHER CONSIDERATIONS

Use of Deception

Investigators should disclose as much information to the subject as possible in regard to all procedures, risks, benefits, and conditions of participation in alcohol research. It is recognized that some alcohol research studies require elements of deception about study procedures. If a deceptive procedure is proposed, the full extent and rationale for employing the deception should be made explicit in the protocol, and the absence of any alternative approach should be documented.

Where possible, informing the subject that the research protocol may include elements intended to deceive, and providing as much information about the nature of the possible deception, is encouraged. In any case, the informed consent statement should identify all specific substances that might be administered during the research and a description of maximum exposures (peak concentration, duration of exposure) that could be experienced by participating. Subjects should be debriefed at the earliest scientifically appropriate time possible.

Alcohol Exposure Levels

Researchers need to consider a potential subject's customary drinking history when establishing exclusion criteria for a given experiment. In general, it is not recommended that alcohol be administered at a level that would result in higher BACs than the subject has reached with self-administration on at least some occasions in the past year. The extent to which one's customary drinking level might be exceeded in the laboratory is one of degree, and risk/benefit issues must be considered.

In all cases, the exact dosing parameters must be explained in clear and explicit language concerning the number of drink equivalents, their concentration, their total volume, and the amount of time allotted for administration and included as part of the informed consent procedure. The subject should also be informed about the range of peak blood alcohol concentrations that people of his/her total body water (a published function of the subject's age, height, weight and gender) might achieve with the administration planned. Coupled with this, care should always be taken to ensure that subjects do not feel coerced or subtly pressured to consume more alcohol than they feel comfortable consuming or that administration of the alcohol will not be at greater levels than that with which subjects are comfortable. Subjects should always feel free to not ingest the entire dose provided to them or to stop the administration of alcohol at any time.

Ad libitum administration studies, in which subjects control the rate and quantity of alcohol administered, can present unique safety challenges. Although one might expect subjects in *ad libitum* administration studies to drink within their customary levels, some experimental manipulations (e.g., modeling by a heavy drinking confederate or other subjects) are known to have large effects on drinking and could be expected to unduly influence subjects to drink more than they might otherwise. For this reason, in ad libitum drinking studies, the maximum peak blood alcohol concentration that a subject might achieve should limit the amount of alcohol consumed, based on the individual's total body water estimate.

Access to Medical Backup Services

The potential for adverse medical consequences of alcohol administration varies substantially in association with the age, drinking status, and physical and emotional health of the subjects, and also with the route of administration, total dose, and time course of alcohol exposure. The concern may be compounded by the co-administration of any other drug with alcohol. Assessments of risk should include considerations of such experimental parameters when characterizing potential adverse consequences in the proposed research. A thorough analysis of how the risks are to be minimized would include an assessment of the need for medical backup services, as well as a description of how services will be obtained if needed.

Post-administration Considerations

Subjects should be informed of the likely duration of their participation in the session, taking into account the estimated length of time for the subject's BAC to return to the pre-determined threshold for release (typically between 0.02g% and 0.04g%). Investigators should ensure that subjects understand any restrictions on transportation from the laboratory following the conclusion of their session.

Adequate accommodation of subjects while in the laboratory requires the following:

- A comfortable area to wait and rest with nearby bathroom facilities that do not require unnecessary effort to access (for example, on the same floor).
- Ability to monitor subjects on a continuous or near-continuous basis in a way that is not intrusive.
- Ready access to emergency care without leaving the subject alone.
- Medically trained personnel on site are not required for most studies involving ethanol administration unless there is reason to expect a high likelihood of adverse medical effects.

Investigators should caution subjects regarding activities following the sessions. Release BAC values should be confirmed by at least two readings.

Follow-Up

Follow-up assessments of delayed reactions to alcohol administration may be appropriate in some circumstances, such as when subjects are alcohol-dependent or when the subject experiences an adverse reaction during the session.

Compensation for Participation

Compensation should not be given at a level or in a form that could be considered to be coercive. Deciding upon the form of compensation to be given to research subjects for their time and inconvenience presents unique problems for researchers administering alcohol to human subjects. Determining if a specific type of compensation should be offered could depend on whether the research takes place in the context of the subject's own treatment for alcohol related diseases or other disease, or is part of more generalized research into the public health aspects of alcohol. The form of compensation might be dependent on the particular groups to which the subjects belong.

VI. GLOSSARY

Age of legal drinking: The minimum age at which a person may legally purchase alcohol. Currently, all fifty United States have a statute setting 21 years of age as the minimum age. However, some states have created specific statutory exceptions to allow the sale and serving of alcohol to those under 21.

Age of majority: The age when a person acquires all the rights and responsibilities of being an adult. In most states, the age is 18.

Assent: Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Consent: An agreement to do something or to allow something to happen, made with complete knowledge of all relevant facts, such as the risks involved or any available alternatives.

Debriefing: Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)

DOJ Common Rule: The Common Rule applies to all federally funded research conducted both intra- and extramurally. The rule directs a research institution to assure the federal government that it will provide and enforce protections for human subjects of research conducted under its auspices.

Health Information Portability and Accountability Act Privacy Rule: The Standards for Privacy of Individually Identifiable Health Information, or Privacy Rule, establishes a set of national standards for the protection of certain health information. A major goal of the Privacy Rule is to assure that individuals' health information is properly protected while allowing the flow of health information needed to provide and promote high quality health care and to protect the public's health and well-being.

Human Subjects: Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information.

Legal Guardian: A person who has the legal responsibility for providing the care and management of a person who is incapable, either due to age (very young or even very old, or to some other physical, mental or emotional impairment, of administering his or her own affairs.

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