NACDA Guidelines for Substance Abuse Research Involving Children and Adolescents

I. Preamble

The National Advisory Council on Drug Abuse (NACDA) recognizes that substance abuse research involving children and adolescents is vital to understanding factors contributing to the initiation, maintenance and cessation of substance use and abuse among this population. This period of life is characterized by growth and maturation of brain and body, which potentially affects responses to drugs and treatment. Moreover, the great majority of people who develop substance use disorders (SUDs) or addiction begin to use drugs when they are young. Therefore, study of this population is crucial in order to develop effective prevention and treatment interventions, both behavioral and pharmacological, for youth.

Research on substance abuse involving children/adolescents should be designed, reviewed and conducted within the broader ethical principles outlined in the Belmont Report (discussed in greater detail in the NACDA Guidelines for Administration of Drugs to Human Subjects; http://www.drugabuse.gov/Funding/HSGuide.html) and the Code of Federal Regulations 45 CFR Part 46 Subpart A, and the additional protections for children under Subpart D. The reader is also referred to the general guidelines that have been developed specifically for the pediatric population: Guidelines for Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (RE9503), American Academy of Pediatrics, Committee on Drugs (http://aappolicy.aappublications.org/cgi/reprint/pediatrics;95/2/286); Ethical Standards for Research with Children, Society for Research on Child Development (http://www.srcd.org/ethicalstandards.html); Institute of Medicine, The Ethical Conduct of Clinical Research Involving Children (http://www.iom.edu/report.asp?id=19422); and Shah, S, Whittle, A, Wilfond, B., Gensler, G., & Wendler, D. (2004) How do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research, JAMA, 29 (4), 476-481.

II. Purpose of These Guidelines

Research on substance use and abuse among children and adolescents presents its own unique challenges. As a result, the National Advisory Council for Drug Abuse (NACDA) and the National Institute on Drug Abuse (NIDA) have developed these guidelines to assist researchers, institutional review boards and study reviewers in developing, conducting or reviewing studies involving children and adolescents. The guidelines that are provided in this document address both general issues regarding conducting research in youth as well as issues that may specifically arise when conducting drug abuse research in youth. *These guidelines are not codified and do not constitute Federal regulation.* These guidelines are not intended to supplant the functions of either the Institutional Review Board (IRB) or the Office for Human Research Protections (OHRP). They are advisory to applicants, IRBs, Integrated Review Groups (IRGs), and others.

III. General Issues

The NACDA recommends consideration of a number of general issues applicable to studying substance use and abuse in children/adolescents. These issues are:

A. Federal Regulations for conducting research involving children

The regulations require that an Institutional Review Board (IRB) reviewing research involving children as subjects consider "the risks of harm or discomfort inherent in the proposed research and the anticipated benefits to the child subjects or society in general (OHRP, 2001)." The regulations do not include as research risks any risks the child would be exposed to as part of clinical care. Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" (45 CFR 46.402). For most states, under most conditions, this legal age is 18 years old* (for exceptions, see section entitled "Consent from Minors").

To receive IRB approval, the proposed research must fall into one of four categories.

1. Research not involving greater than **minimal risk** (45 CFR 46.404).
2. Research involving greater than minimal risk but presenting the **prospect of direct benefit** to the individual subjects (45 CFR 46.405) 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 alternative approaches; and
    c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
3. Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406). Research in this category is approvable provided:
    a. The risk represents a **minor increase over minimal risk;**
    b. The research intervention/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/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.
4. Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407). Research that the IRB finds does not meet the requirements of 45 CFR 46.404, .405, .406, may be supported by DHHS provided:
    a. The IRB finds the research presents a reasonable opportunity to further 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 and following an opportunity for public review and comment, determines that the research satisfies one of the 45 CFR 46.404, .405, or .406 categories or the research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and will be conducted in accordance with sound ethical principles, and adequate provisions are made

*(Please note that for NIH-funded clinical research, children are defined as individuals "under the age of 21"; however individuals between the ages of 18 and 21 are permitted to consent to participate in research.)

for soliciting the assent of children and the permission of their parents or guardians.

Minimal risk (See Box)
Minimal risk is defined as the level of risk where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102.i)." General consensus in the literature is that the risks of daily life refer to the daily lives of **normal, average, healthy** children living in safe environments and should be considered using rational means.

Minor increase over minimal risk
A minor increase over minimal risk is not defined in the regulations. "The Office for Human Research Protections, Department of Health and Human Services, believes that it is an appropriate responsibility of the IRB to determine when research would involve a minor increase over minimal risk" (Stith-Coleman, OHRP, personal communication). The statement in the regulations that "the research intervention/procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical situations" suggests that "minor increase over minimal risk" could be a relative standard, i.e. a minor increase over the risk that a child with this "condition" is exposed to in daily life. While no guidelines have been issued by OHRP on whether or not "minor increase over minimal risk" should be an absolute or relative standard, both the IOM (2004) and the Secretary's Advisory Committee on Human Research Protections (SACHRP) have recommended that a minor increase over minimal risk be considered an absolute standard similar to that for minimal risk.

Prospect of direct benefit
Prospect of direct benefit is not defined in the regulations. Direct benefit is usually considered to be medical/psychological benefits from research procedures only. Payments for participation in research or added psychological or medical interventions should not be considered a benefit.

Disorder or condition
The definition of a disorder or condition is not specified in the regulations. The recent IOM report states that limiting the definition of "disorder or condition" to an illness, disease or injury would result in too narrow a definition, whereas broad interpretations of any social, developmental or other characteristic, could unjustly single out groups of children already burdened by social disadvantages for research that would not necessarily benefit them. The IOM therefore recommended that "the term 'condition' should refer to a specific physical, psychological, neurodevelopmental or social characteristic that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future." Therefore, given available scientific evidence, a "condition" may include risk factor(s) associated with a disorder that differentiate individuals from the general population. For example, because studies have demonstrated that exposure to trauma increases an individual's risk for substance abuse; children exposed to trauma may be considered to have a "condition" predisposing them to substance abuse.

Box. Federal Risk and Benefit Categories for Pediatric Research

Prospect of Direct Benefit

Minimal Risk* Approvable by an institutional review board (IRB) provided:
• Parental permission†
• Child's assent‡

Minor Increase Over Minimal Risk Approvable by an IRB provided:
• Risks are "justified" by the anticipated benefit
• Risk-to-benefit profile is at least as favorable as the available alternatives
• Parental permission†
• Child's assent‡

More Than a Minor Increase Over Minimal Risk Approvable by an IRB provided:
• Risks are "justified" by the anticipated benefit
• Risk-to-benefit profile is at least as favorable as the available alternatives
• Parental permission†
• Child's assent‡

No Prospect of Direct Benefit

Minimal Risk* Approvable by an IRB provided:
• Parental permission†
• Child's assent‡

Minor Increase Over Minimal Risk Approvable by an IRB provided:
• Intervention is reasonably commensurate with subjects' actual or expected experience(s)
• Intervention is likely to yield generalizable knowledge about subjects' disorder or condition , which is of critical importance for the understanding or amelioration of the subjects' disorder or condition
• Parental permission†
• Child's assent‡

More Than a Minor Increase Over Minimal Risk Not approvable by an IRB§

*Means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (§46.102 [i]).

†Permission of 1 parent is sufficient for minimal risk and prospect of direct benefit research; permission of both parents is required in all other cases, if both are reasonably available. Parental permission may be waived if the IRB makes the findings under 45 CFR 46.116 (c) or (d) or judges that it is not a "reasonable requirement to protect the subjects" (§ 46.408 [c]).

‡May be waived if the IRB judges that the children are not capable of providing assent, or 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" (§46.408 [a]). Assent may also be waived under the provisions of 45 CFR 46.116 (c) and (d).

§May be approved by the Secretary of the Department of Health and Human Services after consultation with a panel of experts and public review and comment, if the research satisfies the conditions of 45 CFR 46.404, .405, or .406 or (i) offers a "reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children" (§46.407), (ii) will be conducted in accordance with sound ethical principles, and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

Source: Modified from Shah et al., 2004; JAMA 291:476-82.

B. Participant informed consent/assent

Assent is defined as a "child's affirmative agreement to participate in research" and applies to children whom the IRB judges to be capable of providing assent. General consensus appears to be those children who have reached an intellectual age of 7 years old, however a precise age has not been specified in the regulations. Therefore, the IRB must make a determination about the appropriate age for obtaining assent. In order to ensure that the subject is able to make an informed voluntary decision, the study should be explained to the child/adolescent at a level that is understandable to the individual, taking into account age, maturity, psychological state, and English language proficiency. The process should provide an opportunity for the minor to express willingness or unwillingness to participate. Care must be taken to ensure that the process is free of coercion from parents and investigators. When the research context may compromise the voluntary nature of assent, particularly in vulnerable populations or in extremely sensitive situations, IRBs may consider the appointment of a participant advocate (an individual with no relationship to the research itself or the family of the participant, however, not necessarily a legal guardian) (Fisher et al., 1996).

It is critical to make sure that all children understand what is involved in the research study for which the investigator is trying to get assent. There are several ways to accomplish this. For example, the investigator may ask the subject to read the consent form aloud. Alternatively, to avoid embarrassment due to problems with reading or comprehension, a video or pictures may be used. The researcher can then discuss the content of the study with the minor, as well as ask questions about relevant content regarding the study. For laboratory studies or clinical procedures, actual demonstration, video or pictures of the procedures should be considered (e.g. simulation of the experience of being in an MRI machine). The capacity for decision-making may also be affected by substance use or abuse or co-morbid disorders. Every effort must be made to develop procedures that document competence in understanding the study procedures and the risk/benefits of participating in the study. For example, procedures should be in place and staff should be qualified to determine that the potential participant is not under the influence of drugs or alcohol, under undue stress because of withdrawal, or otherwise impaired in their cognitive or decision making abilities while giving consent/assent.

Although typically consent/assent should be obtained before an individual is allowed to participate in a study, it is important to remember that an individual has the right to withdraw from a study at any time without penalty or loss of benefits. Therefore, procedures should also be in place that allow for the continued monitoring and ensuring of consent/assent to participate in research that is ongoing.

Waiving assent

The IRB can waive the assent requirement, as it can waive consent requirements, when it finds that (1) the research involves no more than minimal risk to the subjects; (2) the waiver will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116 (d)).

Specifically with respect to waiving the assent of minors, 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 interventions or procedures involved in the research hold 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 can be waived (45 CFR 46.408 (a)).

Consent from minors

Under applicable state law, emancipated minors are able to give independent consent. These minors have become emancipated for various reasons such as judicial decree, marriage or parenthood. They typically are financially independent and live away from home. The mature minor "is usually defined by state law as a minor that is near the age of maturity, displays sufficient understanding of medical procedures, and can be medically emancipated in the treatment of certain conditions, including venereal disease, pregnancy, and drug abuse" (American Academy of Pediatrics, 1995). This legislation was intended to ensure that adolescents would not be deterred from seeking treatment (Levine, 1995). Because Federal regulations define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted," when state law allows minors of a specified age to consent to treatment for substance abuse, for example, these minors are no longer considered "children" for the purposes of research involving treatment for substance abuse. They, therefore, also have a legal right to consent to participate in a substance abuse *treatment* research protocol without the permission of a parent (Brody and Waldron, 2000; English, 1995). This exception only holds for research on a treatment for which they have a legal right to consent without parental permission. If the research protocol involves any procedure not related to this treatment, parental permission is required. Therefore, minors may not be able to consent for research procedures that are "add-ons" to the treatment. For example, a study examining whether a specific treatment works to prevent substance abuse, may require blood tests or behavioral assessments that are only used as research tools to determine the adequacy of the treatment. Procedures introduced solely for research purposes (1) must be considered separately from the treatment itself and (2) depending upon the relevant state law may not be allowed without parental permission. For more information on individual state laws regarding consent from minors, please see the Institute of Medicine Report, "The Ethical Conduct of Clinical Research Involving Children," Appendix B.

Obtaining permission from the emancipated or mature minor to inform parents about the study is preferred. However, in studies which involve minimal risk or in which benefits can be directly derived for the child, informing parents or informed permission from parents may not be necessary. Nonetheless, because participation in treatment studies may involve different and potentially greater risks than standard treatments, parental permission is recommended.

Incarcerated children

In addition to the Federal regulations providing additional protections for children in research, if the research subjects to be studied are incarcerated minors, the research must comply with Federal regulations for research involving prisoners outlined in 45 CFR Part 46 Subpart C. According to Subpart C, "prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass 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." Juveniles court-ordered to a residential treatment facility in lieu of incarceration are also considered "prisoners." This definition does not include individuals released from prison to a halfway house, those court-adjudicated to attend non-residential treatment programs or probationers and parolees. Any HHS-conducted or supported research involving prisoners must be certified by OHRP under Subpart C. In addition, if a research subject becomes incarcerated during the course of a study that was not previously approved in accordance with the requirements of Subpart C, appropriate certification must be provided to OHRP as soon as possible. For additional information, please see the OHRP Guidance on Research Involving Prisoners at http://www.hhs.gov/ohrp/humansubjects/guidance/prisoners.htm.

Wards of the state

Research may be conducted with children who are wards of the State or any other agency provided 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. If the research falls into one of these categories, an advocate must be appointed for each child who is a ward, in addition to any individual acting on behalf of the child as guardian or in loco parentis. This individual must have background and experience in acting in the best interests of the child and must not be associated in any way with the guardian organization (45 CFR 46.409).

C. Parental permission

Because parents/guardians are responsible for protecting the children under their care, permission must be obtained from them to involve their children in a research protocol (except for emancipated minors as discussed above), even in the rare instance when a minor gives assent but a parent does not consent to permission. For research involving no more than minimal risk or involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects, permission from one parent is sufficient. For other categories of research permissible under Subpart D, permission generally must be obtained from both parents, 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.

Parental permission may be a particular challenge if the parent(s) experience problems with substance abuse, co-morbid disorders or associated consequences of substance-abuse including instability in their life circumstances. Therefore, parental permission must give adequate consideration of the mental and physical state of the individual in terms of their ability to fully understand the context of the informed consent document. In addition, the motives of the individual must also be considered. If there is a question about the parent or guardian's ability to give permission, procedures should be in place to evaluate the parents ability to give or maintain permission, for example by a qualified independent third party. If the parent or guardian is deemed unable to give or maintain permission, the participant should be excluded from the study. Parental permission may be waived under the same conditions that allow waiver

of consent as specified in 45 CFR 46.116 (c) and (d) and discussed above in Section III B "Waiving assent."

D. Coercion and undue inducement

The issue of coercion is another area that may be especially salient among this population. Coercion comes in many forms. Fear of expulsion or incarceration cannot be used to coerce minors into participation. In situations where no treatment is readily available or treatment is cost prohibitive, and participating in a treatment study is the only access to treatment, parents may pressure their children to participate. Therefore, acquiring assent is critical for determining the willingness of a child to participate. Finally, the potential for remuneration may also be a factor leading to parental coercion for participation. Financial compensation to parents for their child's participation in a study should be commensurate with the requirements of the study (i.e. for effort, time and inconvenience of the research), as long as no "undue inducements" are offered to lure people into participating who would otherwise choose not to expose themselves to research risks and incentives are not included as a "benefit" in risk-benefit analyses. Children may also be compensated for participation, preferably with incentives other than money (e.g. vouchers)**.** Offering evening or weekend hours and on-site childcare may assist parents who are concerned about lost wages to circumvent the need for monetary compensation.

E. Confidentiality

Investigators should be aware that once information from a drug-abusing youth is placed in the patient records, such records must be handled with extreme confidentiality, beyond those for other medical or research records. Investigators and IRBs should be aware that special federal requirements might apply to certain drug abuse records in research. Information about this may be found in the Code of Federal Regulations (CFR) under 42 CFR Part 2 (http://www.access.gpo.gov/nara/cfr/waisidx_02/42cfr2_02.html), "Confidentiality of Alcohol and Drug Abuse Patient Records" and, for covered entities, in the Privacy Rule under the Health Insurance Portability and Accountability Act (HIPAA - http://www.hhs.gov/ocr/hipaa/).

Certificates of Confidentiality

To ensure that an investigator may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify individuals who are the subject of biomedical, behavioral, clinical or other research, the Secretary of the Department of Health and Human Services (DHHS), may authorize persons engaged in such research to protect the subjects' privacy through a Certificate of Confidentiality obtained from the National Institute on Drug Abuse (42 CFR Part 2a - http://www.access.gpo.gov/nara/cfr/waisidx_02/42cfr2a_02.html). However, certificates of confidentiality do not apply to mandated reporting requirements such as physical or sexual abuse or neglect. For more information on obtaining a Certificate of Confidentiality from NIDA, please visit the NIH Certificate of Confidentiality Kiosk at http://grants2.nih.gov/grants/policy/coc.

Confidentiality from parents

Because of the nature of the population and the subject matter to be studied, confidentiality is a particularly sensitive issue. Assurances of confidentiality must be given to the child/adolescent study participant as well as the parents or whatever other parties (e.g., schools) are involved. If children are excluded from a study because they do not satisfy eligibility requirements that include sensitive information about the child, investigators may not disclose these requirements to parents to protect the confidentiality of the child. During the consent/assent process, all parties should be informed that all information collected during the study remains confidential, and therefore not disclosed to the parent/guardian, including the use of illegal drugs, unless there is a risk of imminent danger to the child or to others, such as suicide or homicide. Given the nature of drug abuse research, there is an inherent danger to research participants who abuse drugs. However, determining whether or not this danger is imminent and, thereby, permitting disclosure of confidential information, is more complicated. There are a number of factors to consider, including whether or not the research participant is in treatment, which drug or drugs are being abused and by what route of administration, the presence of comorbid psychiatric conditions, and the age of the minor. Currently, there are insufficient data to provide specific guidelines on all situations that constitute imminent danger; therefore, we rely on the judgment of the investigator in consultation with their IRB. Moreover, the differentiation between use of drugs and imminence of serious harm resulting from the use of drugs should be clearly stated to the participants, individuals who have signed the informed consent, and relevant parties. The consent form should explicitly state what information may and may not be disclosed to the parent, child, or a third party such as a physician or mental health professional. The consent form should also clearly specify that the release of information to the parents or other parties would only occur with the permission of the minor, except in the case of an adjudicated youth or the need to report withdrawal from the study to the referring agency. If relevant to the study, parents must be made aware that information on their own drug use or psychiatric history (or any other of their children who are minors) will be collected during the course of the study, but also kept confidential. Furthermore, both parties must be made clearly aware that any other mandated information such as domestic physical abuse, sexual abuse or neglect, and information on communicable sexually transmitted diseases will be reported to relevant agencies according to State law. *Other than the mandated information, the final decision regarding the release of information to the parents resides with the investigator, even with signed authorization of the minor (Code of Federal Regulations, Title 42, 1995).*

F. Community consultation

Given the sensitive nature of research on substance abuse involving children or adolescents, particularly that which doesn't present direct benefit to the child, it may be beneficial to establish an advisory board, including members of the community and advocacy groups, at the early stages of developing a research protocol (American Academy of Pediatrics, 1995). Issues of race, ethnicity, socioeconomic status and institutionalization that characterize a study population and issues of potential stigmatization should be considered at all stages of research design, development, and implementation.

IV. Specific issues

The NACDA recommends that these specific issues be considered in the development and review of research studies involving children/adolescents.

A. Criteria for stopping a study

Prior to the initiation of a study, procedures for monitoring research subjects and clear criteria for when the study should be stopped due to increased levels of risk or decreased benefit should be established. Whereas such criteria are typically established for pharmacotherapeutic studies, they should be established for behavioral research as well. One example in which the level of risk changed during a behavioral intervention study was when iatrogenic effects were observed during the course of group therapy with adolescents who engage in high-risk behaviors (Dishion et al., 2001). This study demonstrates the need to set specific criteria for increased risk/decreased benefit that will result in termination of any research study involving children. In addition, for pharmacological interventions, stopping rules should be in place for when there is incontrovertible evidence of benefit. This will necessitate an interim analysis with specific stopping rules for the Data Safety Monitoring Plan (DSMP) or Board (DSMB).

B. Competence of study staff

Sufficient expertise in child development, psychopathology and ethical conduct of research with children and adolescents should be represented among the research staff.

C. Follow-up and referral

Because children and adolescents are considered to be a vulnerable population, careful monitoring and follow-up of this population is essential. In addition, if the adolescent or child is actively using substances, regardless of the type of study, a mechanism for referral to treatment should be established. Furthermore, for subjects in treatment studies that do not have access to treatment outside of the study, continued support should be identified and a concrete viable referral made prior to the end of the study.

D. Incidental clinical findings

During the course of a study, information may be obtained that is clinically meaningful, which is not directly addressed by the research protocol. For example, if an MRI is performed, information may be obtained indicating a previously unknown or undiagnosed medical problem. Similarly, in collecting information about a person's physical or psychological history, unexpected clinical findings may be made. It is important that the researcher state ahead of time how such information will be handled. To this end, and to the extent that the nature of such information can be predicted, the consent form should clearly stipulate what kind of incidental clinical findings will be provided and to whom. Should the circumstances or assumptions surrounding such provisions change significantly during the course of the study, the investigator should consider the introduction of appropriate changes in the consent form.

E. Studies involving administering drugs of abuse to youth

The NACDA Guidelines for Administration of Drugs in Human Subjects discuss issues that arise in research involving the administration of drugs with abuse/dependence liability, and

identify issues to be considered in the development and review of research protocols involving drug administration to human subjects. The investigator is referred to this document on NIDA's website, http://www.drugabuse.gov/Funding/HSGuide.html.

Because adolescence is a period of heightened vulnerability to drug abuse and also a time of dramatic changes in brain and behavioral development, there may be compelling reasons to study how drugs of abuse specifically and/or uniquely affect young people. For studies that involve administration of drugs with abuse liability to youth, the decision to conduct a specific study will need to be made on an individual basis, carefully balancing the risks and benefits to participants. Some of the issues to consider in making this determination are the following: Are there sufficient safety data in adults or older adolescents (18-21 years) to warrant conducting the study in younger subjects? What is the most appropriate recruitment population? What is an acceptable level of risk for adolescents in a drug study? Will exposure under experimental conditions lead to future use? Will exposure send the wrong message about drug use? What are the risks associated with the administration of a drug to a youth, in light of ongoing developmental changes? For these sorts of questions, follow-up data collection would be critical. Who is responsible for the adolescents' safety, during the study, to and from the study, and after the study? What is the balance between confidentiality and investigator obligations within statutory regulations? What are the appropriate doses to use in youth? Consideration must be given to prior history of drug use, and family history of drug or mental health problems. Statutory regulations both among states and local authorities must be given careful attention.

Currently, NIDA does not fund any research in which drugs of abuse are administered to minors (including those who are current drug users). However, because of the importance of improving our understanding of how drugs of abuse affect the developing brain and behavior, future research questions may require such studies to be considered. Investigators should note that because the administration of drugs with abuse liability to children or adolescents may pose greater than a minor increase over minimal risk and no prospect of direct benefit, such protocols will most likely fall under 45 CFR 46.407. In order to provide better guidance and to emphasize the significance of considering specific issues during the development and review stage of such proposals, two examples of NIH-supported protocols, that have recently or are currently under review by DHHS according to 45 CFR 46.407, are described below.

1. "Alcohol, Sleep and Circadian Rhythms in Young Humans, Study 2 - Effects of Evening Ingestion of Alcohol on Sleep, Circadian Phase, and Performance as a Function of Parental History of Alcohol Abuse/Dependence" (funded by NIAAA). This protocol proposes to study the effects of a small or moderate evening dose of alcohol on sleep, waking performance, and circadian phase in a total of 64 adolescents (15 to 16 years of age) and young adults (21 to 22 years of age), and examine how the effects may differ between individuals who have a parent with a history of alcohol dependence and those who do not. The final recommendation by OHRP was that "HHS defer support for the proposed research involving the enrollment of 15- to 16-year old subjects…" because "adequate justification has not been provided…OHRP notes that ongoing IRB-approved studies under the grant will provide data relevant to both the safety of study subjects and the scientific rationale for involving 15- to 16-year old subjects. Upon completion of …ongoing research on adults…re-review of the proposed research would be warranted

to consider extending the research to 15- to 16-year old subjects." The Acting Assistant Secretary for Health, HHS approved these recommendations.

2. "Effects of single Dose of Dextroamphetamine in Attention Deficit Hyperactive Disorder: A Functional Magnetic Resonance Study" (funded by NIMH). This study proposes to investigate the pathophysiology of ADHD by imaging the brain response to amphetamine of children with ADHD compared to healthy children. The study is clearly of high significance since there is great public interest in the matter of stimulant treatment of ADHD. Because amphetamine would be administered to healthy children, this protocol was forwarded to, and is currently under review by, the OHRP under 45 CFR 46.407.

F. Neuroimaging

There are two categories of imaging techniques that can be used to investigate predispositions to and the effects of drugs of abuse; those that utilize magnetic fields such as functional magnetic resonance imaging (fMRI) and those that use ionizing radiation such as positron emission tomography (PET) and single photon emission computed tomography (SPECT).

There are three primary types of risks associated with PET and SPECT studies in minors, the stress associated with the procedure, the risks associated with arterial cannulation required by some studies to quantify radiotracer delivery, and the side effects associated with exposure to ionized radiation. Stress risks can be diminished by familiarizing children with the procedure by role rehearsal prior to the study or exposure to a simulated scanning device. The risks of arterial cannulation include mild-to-moderate pain, bruising at the puncture site, and spasm or clotting of the artery with a temporary decrease in blood flow. In rare instances blocking of the artery, poor healing, or infection at the catheter insertion site may occur. Permanent damage is extremely rare.

The risks of greatest concern have been those that are associated with radiation exposure such as potential carcinogenic effects or increased incidence of genetic mutations. According to the Federal Drug Administration Guidelines for use of radioactive drugs for research (21 CFR 361), "a single radiation dose for a research subject under 18 years of age to the whole body, active blood-forming organs, lens of the eye and gonads shall not exceed 0.3 rem and the annual total dose should not exceed 0.5 rem. For all other organs, a single dose cannot exceed 0.5 rem and the annual total dose cannot exceed 1.5 rem."

Exposure to radiation through neuroimaging research constitutes *more than a minor increase over minimal risk*. Therefore, this research would be approvable by an IRB only if study participants could *directly* benefit from the research. For all others, including healthy controls, this type of protocol would have to be reviewed under 407 provisions, thus could only be done if approved at the Department level. In addition, since the risks for radiation appear to reflect cumulative effects, cumulative exposure should be considered when determining whether the risk is justified by the anticipated benefits, particularly if repeated use of neuroimaging with radioactive tracers is anticipated in a study.

Because of a lack of radiation exposure, fewer risks are encountered in fMRI studies. One concern with conducting fMRI (as well as PET/SPECT) studies in children, however, is the potential need for sedation to ensure that children remain still during the scans. Sedation presents significant risks due to potential complications such as respiratory distress. An alternative to sedation is to schedule scans for young children during times when children are naturally sleepy. This can also alleviate anxiety due to claustrophobia.

F. Genetics Studies

The primary ethical issues to be considered when undertaking genetics studies are the confidentiality of genetic information and the comprehension of the concepts of risk and probability associated with the identification of susceptibility genes. Genetic information must not be included as part of the medical record which may be subject to requests from insurance companies and employers. Investigators may alternatively determine that genetic information is maintained as part of a research record that is subject to the confidentiality guidelines discussed in the section entitled "Confidentiality" above. In this case, all information collected during the study remains confidential unless there is imminent danger to the child or to others. Since genetic susceptibility to substance abuse would not be considered to pose imminent danger, this information should also remain confidential.

Another concern in genetics studies is the risk of harm resulting from the lack of understanding of genetic findings. For example, subjects/parents may minimize the potential for prevention or behavioral change due to the misconception that genetic susceptibility to substance abuse necessarily means a subject will become addicted. Therefore, care must be taken to ensure that subjects and their parents understand that the genetics related to substance abuse may provide information about increased risk and information on better treatments for the disorder in the future but due to the multifactorial nature of substance abuse, is not deterministic for developing a substance abuse disorder. In many cases, genetic information is not released for this reason or because it is not yet clinically meaningful. If the investigator decides that it is inappropriate to release this information to the subject and/or parents, this should be made explicit during the consent process.

Provisions for removing samples from the study

Investigators must explain to potential subjects and their parents, during the informed consent process, about their options for removing samples from the study. If there is any reason why it may not be possible to remove samples in the future (e.g. DNA in repository that has been de-identified and distributed to other researchers), the timeline and reasons should be clearly elucidated.

Future use of DNA samples

DNA samples that are collected as part of a specific study may also be useful for future research not yet conceived. Consequently, participants may be given the opportunity to allow or deny the future use of their DNA samples for other purposes, or to ensure that personally identifying information is removed from their DNA samples before it is shared with other researchers or used for other purposes.

G. Survey Research

Research involving survey or interview procedures with children is **not** exempt from parental consent regulations (45 CFR 46.401). The No Child Left Behind Act of 2001 (Public Law 107-110 Section 1061) and the Protection of Pupil Rights Amendments (PPRA) delineate consent rules for surveys of students (34 CFR Part 98). Under the current law, if the US Department of Education (DOE) funds a study and the research involves **"protected information,"** then the PPRA afford parents the right to provide active consent. "Protected information" is defined as information on (1) political affiliations of student or student's parent; (2) mental or psychological problems of student or student's family; (3) sex behavior or attitudes; (4) illegal, anti-social, self-incriminating or demeaning behavior; (5) critical appraisals of others with whom students have close family relationships; (6) legally recognized privileged or analogous relationships; (7) religious practices, affiliations or beliefs of student or student's parent; or (8) income. For studies that are funded by sources other than the US DOE (i.e. grants from the National Institutes of Health) and are administered by education institutions that receive funds from any US DOE program (i.e. public schools and some private schools), and that include protected information, parents have the right to inspect the surveys before they are administered and to opt the student out of the survey. The PPRA requires that individual schools adopt policies for consent requirements and IRBs must ensure that investigators use consent procedures that are in accordance with these local policies.

Waiver of parental permission

In some survey studies, specifically those that ask sensitive questions regarding illegal drug use and associated behaviors or environmental circumstances, it may be in the best interests of the study to acquire a waiver of parental permission by the IRB. Collecting this type of information in an anonymous manner may be crucial for detecting the prevalence of drug use and abuse and factors associated with increases or decreases in use. Therefore, field studies, which (1) anonymize the data; (2) pose minimal risk; (3) would be impractical to obtain parental permission (i.e. it would drastically lower response rate); and (4) would bias the results, may receive a waiver of parental permission by the IRB, under the same conditions that allow a waiver of consent as specified in 45 CFR 46.116 (c) and (d) and discussed above in Section III B "Waiving assent."

I. Treatment Studies

Placebo-controlled or untreated controlled studies

Researchers conducting studies of treatment vs. placebo or untreated control groups must evaluate the risk/benefit ratio separately for the treated and untreated groups, i.e., those in the placebo group may not have a prospect of direct benefit whereas those in the treatment group do. Placebo or untreated observational control groups can be used in pediatric studies if their use does not expose children to unacceptable risks. For example, untreated control groups such as waitlist controls must be evaluated to determine the level of risk to which the participant is exposed by not receiving immediate care. In the case of placebo-controlled studies, the risks are acceptable when the potential risk for children in the placebo-control arm is equivalent to that for children receiving standard care or when the potential harms in the placebo control arm are no more than a minor increase over minimal risk. In many such studies, treatment as usual is

included to minimize undue risk in the placebo arm. Clear explanations of the purpose for and the consequences of being assigned to a placebo-control arm should be made during the informed consent process. Moreover, criteria for participant withdrawal, study discontinuation, and monitoring the status of the participant during the clinical trial should be clearly established as part of the research protocol prior to the study's initiation.

Behavioral Interventions

Given the significant problem of substance abuse in youth and the unique considerations in treating this population, the development and testing of behavioral interventions specifically targeted for this population is critical. However, adequate attention must be paid to potential iatrogenic effects that may lead to increased risk for minor subjects so that such studies may be terminated if risk levels change. Therefore, as noted above, criteria for participant withdrawal, study discontinuation, and monitoring the status of the participant should be clearly established prior to the study's initiation and described in the informed consent document.

Pharmacological interventions

New pharmacological interventions are emerging for the treatment of substance abuse, which may be useful in treating youth with substance use disorders. However, developmental differences may cause these drugs to behave differently in children than adults necessitating the study of these therapies in children. Pharmacotherapy studies in children should be performed after efficacy is established in adult Phase II studies. When data for adults are not available, particular care must be taken to justify proceeding with pediatric trials. Moreover, preclinical studies should be conducted using animals, during an equivalent developmental period, to assess potential developmental toxicity and efficacy before trials with children are started.

J. Pathophysiology Studies

Given that substance abuse is a developmental disease, beginning during childhood or adolescence, it is critical that studies of the pathophysiology of substance abuse, such as studies of basic biological mechanisms, are conducted with children. These studies may include those discussed above such as genetics and neuroimaging studies. However, because such studies offer no prospect of direct benefit, only those studies that present no more than a minor increase over minimal risk and are likely to yield generalizable knowledge about the disorder or condition may be approved. Because these studies often do not produce direct or immediate benefits to the participants, they may be the most sensitive and scrutinized types of research conducted in children. The recommendations noted above concerning multi-stakeholder advisory boards and/or consultation with members of the community prior to initiating such research may be particularly applicable to these kinds of scientific projects.

V. References

American Academy of Pediatrics, Committee on Drugs (1995) Guidelines for Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations (RE9503). Pediatrics 95, 286-94.

Brody JL, Waldron HB (2000) Ethical issues in research on the treatment of adolescent substance use disorders. Addict Beh 25, 217-28.

Code of Federal Regulations (2003) Title 21 Part 361.1 Radioactive drugs for certain research uses - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=361.1

Code of Federal Regulations (2003) Title 34 Part 98 Student rights in research, experimental programs and testing (Protection of Pupil Rights Amendments) - http://www.access.gpo.gov/nara/cfr/waisidx_03/34cfr98_03.html.

Code of Federal Regulations (2002) Title 42 CFR Part 2: Confidentiality of Alcohol and Drug Abuse Patient Records - http://www.access.gpo.gov/nara/cfr/waisidx_02/42cfr2_02.html.

Code of Federal Regulations (2001) Title 45 Part 46: Protection Of Human Subjects - http://www.nihtraining.com/ohsrsite/guidelines/45cfr46.html.

Code of Federal Regulations (2002) Title 45 Parts 160 and 164: The Privacy Rule under the Health Insurance Accountability and Portability Act (HIPAA) - http://www.hhs.gov/ocr/hipaa.

Dishion TJ, Poulin F, Burraston B. (2001) Peer group dynamics associated with iatrogenic effects in group interventions with high-risk young adolescents. New Dir Child Adolesc Dev. 91,79-92.

English A (1995) Guidelines for Adolescent Health Research: Legal Perspectives. J Adolescent Health 17, 277-86.

Fisher CB, Hoagwood K, Jensen P (1996) Casebook on ethical issues in research with children and adolescents with mental disorders. In K. Hoagwood, P Jensen and CB Fisher Eds. Ethical issues in research with children and adolescents with mental disorders (pp 135-238). Hillsdale, NH: Erlbaum).

Institute of Medicine (2004) The Ethical Conduct of Clinical Research Involving Children - http://www.iom.edu/report.asp?id=19422.

Levine RJ (1995) Adolescents as research subjects without permission of their parents or guardians: ethical considerations. J Adol Health 17, 287-97.

National Advisory Council on Drug Abuse (2000) Guidelines for Administration of Drugs to Human Subjects - http://www.drugabuse.gov/Funding/HSGuide.html

Office of Human Research Protections (2001) Protections for Children in Research: A Report to Congress in Accordance with Section 1003 of P.L. 106-310, Children's Health Act of 2000.

Public Law 107-110 Section 1061 (2001) The No Child Left Behind Act - http://www.ed.gov/policy/elsec/leg/esea02/107-110.pdf

Shah S, Whittle A, Wilfond B, Gensler G, Wendler D (2004) How do institutional review boards apply the federal risk and benefit standards for pediatric research? JAMA29, 476-82.

Society for Research on Child Development (1991) Ethical Standards for Research with Children, Society for Research on Child Development - http://www.srcd.org/about.html.