NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

The mission of the NIDA is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy. For additional information about areas of interest to the NIDA, please visit our home page at http://www.nida.nih.gov/.

Phase II Competing Renewal Awards

(See http://grants.nih.gov/grants/guide/pa-files/PA-06-036.html.)

NIDA will accept competing renewal Phase II SBIR/STTR grant applications from Phase II SBIR/STTR awardees to continue the process of developing products that require approval of a Federal regulatory agency. Such products include, but are not limited to: medical implants, drugs, vaccines, and new treatment or diagnostic tools that require FDA approval. This renewal grant should allow small businesses to get to a stage where interest and investment by third parties is more likely.

Please contact Dr. Cathrine Sasek (contact information provided below) before beginning the process of putting an application together. Prospective applicants are strongly encouraged to contact NIH staff prior to submission of a type 2 competing renewal application. Prospective applicants are strongly encouraged to submit to the program contact a letter of intent that includes the following information:

- Descriptive title of the proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Funding Opportunity Announcement Number (e.g., PA-08-XXX)

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIH staff to estimate the potential review workload and plan the review. It is expected that only a portion of NIDA SBIR/STTR Phase II awards will be eligible for a competing renewal grant.

The following examples would make appropriate topics for proposed SBIR or STTR Phase II competing renewal projects. These are meant for illustrative purposes only and are not exclusive of other appropriate activities.

Research and development efforts can be focused on medications for the treatment of cocaine, methamphetamine, and other stimulant abuse, as well as towards opiate, cannabis, PCP and club drugs. The medications under development should be targeted towards attainment of abstinence, maintenance, and/or relapse prevention.

- Preclinical studies, including pharmacology and toxicology, beyond those conducted under the initial SBIR Phase I and Phase II grants. The studies conducted under the previous grants should be sufficient to provide a sound rationale for continued development of the entity or entities.

- Completion of studies as required by the FDA for an IND application.
- Human laboratory clinical trials to determine a medication's safety profile, metabolism, cardiovascular effects, interaction with drugs of abuse, etc.
- Clinical studies to assess the efficacy of the medication under development.

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Division of Basic Neuroscience and Behavioral Research (DBNBR)

DBNBR's basic neuroscience and behavioral research focuses on understanding the mechanisms, characteristics, and processes of drug abuse both in adult and developing organisms. Basic behavioral, cognitive, neurobiological, cellular, molecular, chemical, and genetics research aims at characterizing and understanding drug seeking, compulsive behavior, and addictive processes. These research areas necessarily include studies of normal processes. Using both animal and human studies, basic behavioral research focuses on behavioral and cognitive processes that may or do lead to drug initiation, and the behavioral and cognitive consequences of drug abuse. Neurobiology research focuses on the neural mechanisms and substrates underlying behavioral and cognitive processes and vulnerability factors associated with drug abuse, addiction, sensitization, tolerance, and relapse. DBNBR also supports basic chemistry and pharmacological studies focusing on structure/activity relationships, definition, and characterization of systems involved in drug actions, chemical synthesis of new ligands, pharmacokinetics, analytical methods, understanding basic mechanisms of drug action and drug testing. The focus of maternal and paternal drug use is to ascertain the consequences of drug exposure on brain development as well as on other physiological systems.

Computational and theoretical modeling of biological systems and behavioral processes, biomedical computing and/or information science and technology development is supported by DBNBR.

1. *Metabolomics in Drug Abuse Research.* Metabolomics is the study of all molecules of a cell or organism and their identification and quantification that helps to understand the cellular regulation, metabolic pathways and activity and response under normal and other conditions. This technique thus could be used to develop metabolic profiling of normal or healthy subjects and subjects under the influence of substances of abuse or those undergoing drug rehabilitation programs.

   NIDA is looking for proposals on development of novel metabolomics technologies toward practical application in pathway and network investigation in biological systems particularly in understanding the mechanisms of drug addiction and discovering biomarkers for developing treatment for drug addiction.

   Phase I proposal should demonstrate the feasibility of developing new metabolomics technology and phase II should focus on the application of this technology in drug abuse research.

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2. *Development of Alternate Drug Delivery Dosage Forms for Drugs Abuse Studies.* The SBIR proposals are being solicited to design and develop alternate dosage forms for drugs that are not orally administered such as nicotine, marijuana, heroin, etc. Phase I should demonstrate the feasibility of the proposed innovation and Phase II, the development and testing of the innovation.

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3. *Discovery of New Chemical Probes.* The SBIR proposal are being solicited to discover new chemical compounds as biological probes either by synthesis or isolation from natural resources in studying the mechanisms of action of drugs of abuse. Such substances could be new chemical compounds, drug products, or peptides. Currently there are several ligands available through the NIDA drug supply system such as SR 141716A, SR144528, CP 55,840, anandamide, epibatidine, mecamylamine, SNC 80, NCS-382, U50,488H, DALDA, DSLET, Dynorphins, DALCE, Orphanin FQ, Kaffiralin 1 and 2, etc. All probes for cannabinoids, neuropeptides, nicotinic acetylcholinergic receptors and related probes for drug abuse study are encouraged. In addition proposals on biological screening of such new compounds as potential ligands for drug abuse research will also be considered.

   Phase I should demonstrate the feasibility of the proposed innovation and Phase II, the development, characterization, testing, and screening of innovation. It should also be demonstrated that the new or modified chemical compounds are suitable for drug abuse research.

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4. *Discovery and Study of Psychoactive Components of Botanicals.* NIDA is looking for proposals to develop methods for the isolation, purification, identification and characterization of active and inactive ingredients of herbal plants (stimulants, hallucinogenic, analgesics, and/or narcotics) and evaluation of their biological properties. Such studies may include chemistry, toxicology, pharmacodynamics, pharmacokinetics and the mechanisms of action of active and inactive ingredients to understand their efficacy, usefulness, adverse effects and abuse potential.

   Phase I should demonstrate the feasibility of the proposed innovation and Phase II, the development, characterization, testing, and screening of innovation.

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5. *Virtual Reality for Treatment of Pain.* Virtual Reality (VR) exposure can reduce reported pain during wound care. Grant proposals are sought to examine the utility of VR technologies in the treatment of various types of pain. Development of treatments for both acute and chronic pain is sought. These treatments can be based in clinical settings or the patients' homes. Phase I testing should establish the feasibility of the use of this technology in the particular population to be tested. Phase I should also produce data that demonstrates that this methodology is effective for the particular type of pain being treated. Phase II should involve larger-scale testing (e.g., more subjects and treatment trials) examining various treatment parameters (e.g., timing of treatment, types of VR environments). The focus of Phase II testing should be the refinement of this treatment for use in pain patients.

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6. *Virtual Reality for the Treatment of Drug Abuse.* Virtual Reality (VR) can be a useful clinical tool. In this particular study, VR exposure was used to allow patients to selectively not attend to an otherwise painful procedure. Drug abuse, like pain, is a problem that is strongly impacted by stimuli in the abuser's environment and psychological factors. Thus, it is reasonable to assume that VR may be useful in allowing individuals to ignore drugs cravings, withdrawal symptoms or environmental cues that promote drug abuse. Grant proposals are sought to examine the utility of VR technologies in the treatment of various types of drug abuse. These treatments can be based in clinical settings or the patients' homes. These treatments can be developed to address drug withdrawal, drug craving or on-going drug related behaviors. The development of VR technologies to address abuse of all types of drugs (e.g., cocaine, marijuana, nicotine, alcohol, inhalants) is sought. Phase I testing should establish the feasibility of the use of this technology for the particular drug problem addressed (e.g., cocaine craving, opioid withdrawal) and should also produce data that demonstrates that this methodology is effective for the particular drug problem. Phase II should involve larger-scale testing (e.g., more subjects and treatment trials) examining various treatment parameters (e.g., timing of treatment, types of VR environments). The focus of Phase II testing should be the refinement of this treatment for use in the treatment of drug abusers.

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7. *Development of a Virtual Reality Environment for Teaching about the Impact of Drug Abuse on the Brain.* Virtual reality (VR) is emerging as a technology with a multitude of uses within the medical sciences. In terms of the science of drug abuse, it is being developed as a treatment tool. The current solicitation seeks the development of a virtual reality environment that can be used in educational settings to teach about how drugs of abuse (both illicit and licit) affect the brain and behavior.

   The cost of portable hardware needed to present a VR environment is relatively inexpensive. If education programs like the one sought in this solicitation were available, it is likely that VR would be used as a teaching tool in many settings, including classrooms and museums.

   The particular program sought here is to present an interactive three-dimensional virtual brain that shows normal brain functions and, in contrast, brain function after exposure to drugs of abuse. This technology could illustrate the neurotoxic and long-term effects of drug abuse on the brain. This VR may include other features that are not described above, provided that it will be useful in educating individuals about the medical, behavioral and social effects of drug abuse.

   The phase I proposal should develop a beta version of the program. Further, the phase I application should include a preliminary demonstration of "usability," where it is shown that the types of people being educated with this program (e.g. teachers) can effectively operate this system without extensive training. Further, it should be demonstrated that the hardware is easily worn by subjects, and that the subjects can rapidly understand how to effectively interact in the VR environment.

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8. *Nanoscience-based Design of Therapies for Substance Abuse Treatment.* Nanoscience and nanotechnology, by manipulating matter at the atomic or molecular levels, are emerging research areas that have the potential to fundamentally transform the study of biological systems and lead to the development of new methods for detection, prevention, and treatment of substance abuse and related disease states. NIDA invites nanotechnology-based applications in the following areas:

    a. Methods to enhance the efficacy of FDA-approved compounds by reducing their size to the nanoscale range to alter absorption, distribution, metabolism, or excretion.

    b. Development of new compounds, through manipulation of matter at the atomic or molecular levels that could more readily pass the blood-brain-barrier or cell membranes.

    c. Development of nanoscale particles for controlled targeted delivery of therapeutics, genes, or antibodies.

    d. Methods to enhance existing imaging technologies using magnetic properties at the nanoscale.

    e. Application of nanostructures (e.g. noble metal nanoparticles, quantum dots, and nanolithographic structures that show promise for diagnostic development) for identification and analysis of genes, proteins, and other biological molecules implicated in the actions of drugs of abuse.

    Proposals are invited from any of the above areas. Phase I should demonstrate convincingly the viability of the proposed innovation, whereas Phase II should carry out the development, characterization, testing, and screening of the innovation.

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9. *Functional Genomics Resources and Strategies:* In the post-genomic era, an explosion of gene discovery studies utilizing strategies such as genome-wide association scans, microarrays, and proteomics have identified a host of genes/gene variants associated with susceptibility to, or protection from, diseases of addiction. A critical next step is to validate these candidate genes/variants to determine which ones play an authentic functional role in mediating addiction. Functional validation could occur at many different phenotypic levels ranging from the molecular to the behavioral. Studies could investigate a few high priority genes/variants or could test several hundred genes/variants rapidly. The development of resources and strategies that would facilitate functional validation of genes/gene variants could include (but are not limited to) the following areas:

    a. Gene/variant effects on subcellular localization, stability, or function of mRNAs/proteins relevant to drug addiction.

    b. The development of imaging and other strategies to identify gene/variant effects on neuronal or brain functions relevant to addiction.

    c. Strategies to identify gene/variant effects on behavior, such as response to addictive stimuli, stress, or changes in social situations.

    d. RNA interference-mediated depletion of candidate genes in cells or whole organisms to look for phenotypic alterations such as changes in synapse, dendritic spine, or cell morphology, gene expression, or behavioral responses to drugs of abuse.

    e. Strategies exploiting the growing collection of genetic mutants in candidate genes (particularly utilizing model organisms such as mouse, zebrafish, *Drosophila*, *C. elegans* or yeast) to functionally validate genes/variants.

f. Approaches enabling comparison of wild type protein function to the function of allelic variants using *in vivo* transgenes or *in vitro* biochemical assays, especially if these approaches reveal whether a variation increases or decreases gene function.

g. Systems-based approaches investigating whether a set of candidate genes is co-expressed in a particular brain region or cell type, physically interacts with one another, or functions together in a signal transduction cascade are also of great interest.

h. Approaches to ascribe drug abuse-related function to genes/variants in non-coding RNAs, microRNAs, gene regulatory elements, gene copy number, or other putative non-protein coding regions of the genome.

i. Methods of translating functional studies in model systems to validate gene/variant function in humans.

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10. *Genetic Studies.* The National Institute on Drug Abuse is interested in SBIR proposals that would facilitate the identification of genetic loci that confer vulnerability to substance abuse and addiction. Areas of interest include but are not limited to:

    a. Collection and genotyping of human pedigrees and sib-pairs for vulnerability or resistance to drug abuse.

    b. Isolation and identification of mutant strains in genetic model systems such as Zebra fish, Drosophila, C. elegans, mice, and rats that are more vulnerable or resistant to drugs of abuse.

    c. Design, development, and marketing of behavioral apparatuses to conduct rapid behavioral throughput screens for identifying genetic vulnerability to addiction in genetic model systems.

    d. Development of transgenic models for drug abuse using bacterial artificial or yeast artificial chromosomes.

    e. Development of software and databases for candidate genes for drug abuse.

    f. Identification and mapping of functional polymorphisms of candidate genes for drug abuse.

    g. Placement of candidate genes for drug abuse on biochips.

    h. Marker-assisted breeding of congenic mouse and rat strains for mapping quantitative trait loci associated with addiction and drug abuse.

    i. Vectors for gene transfer into neurons.

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11. *Effects of Drugs at the Cellular Level.* Development of new imaging techniques, reagents and related hardware and software for dynamic investigations of the effects of drugs of abuse on cellular activities and communications. For example, these techniques might include, but are not limited to, development and utilization of reagents for magnetic resonance microscopy and other MRI methods; development of methodologies applying functional MRI to drug abuse studies; the use of dyes, intrinsic signals, and other optical indicators for studying signal transduction mechanisms, the regulatory control of protein

entities (such as phosphorylation), and neuronal excitatory and inhibitory pathways. Areas of interest may include, but are not limited to:

a. Studies using molecular biological techniques to scale-up protein production for investigations aimed at enhancing understanding of the structure, function and regulation of molecular entities involved in the cellular mechanisms through which abused drugs act.

b. Validated in vitro test systems can reduce the use of animals in screening new compounds that may be of potential benefit in treating drug abuse. Test systems are needed to evaluate activity at receptors or other sites of action, explore mechanism(s) of action, and assess potential toxicity.

c. With the recent success in molecular cloning of various drug abuse relevant receptors, enzymes, and other proteins, researchers will elucidate the molecular mechanism of action of these drugs. Studies to generate strains of transgenic animals carrying a gene of interest are solicited. Of special interest are knockout and tissue-specific knockout animals. These animals can be used to identify gene function, and to study the pharmacological, physiological, and behavioral role of a single gene.

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12. *Research Resources.* The National Institute on Drug Abuse is interested in SBIR proposals that would generate the following resources for drug abuse research:

    a. Resources for the application of genetic engineering to dynamically monitor neuronal function.

    b. C57BL6 Mouse embryonic stem cells and spermatogonial stem cells.

    c. Turnkey technology for proteomics such as the development of protein and peptide chips to study drug effects on neuronal mechanisms.

    d. Antibodies, aptamers, ligands, etc. relevant to drug abuse research.

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13. *Computation, Modeling and Data Integration in Drug Abuse Research.*

    a. Development of software or other tools, which enable data integration, and the development of computational models related to addiction and other medical consequences of substance abuse, e.g. tools that enable the integration of proteomics, genomics, transcriptomics, metabolomics and other data into applications leading to systems understanding of drug effects upon biological systems, or developing innovative approaches for managing knowledge and integrating information from text, data, image, and other sources or files generated in addiction research.

    b. Tools, which enable multilevel and multiscale modeling of biological and behavioral systems relevant to substance abuse research, such as those relevant to evaluations of expected utility.

    c. Development of software tools and interactive technologies (such as applications of grid technologies and networked appliances) which enable the prevention, treatment and study of substance abuse as well as the evaluation of prevention and treatment strategies.

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14. *GHB Detection Kits* NIDA is seeking SBIR grant applications for development of diagnostic kits for rapid detection of gamma-hydroxy butyric acid (GHB), gamma-butyrolactone (GBL), and 1,4,-butane-diol (BD) in body fluids (plasma or urine). These three substances are often called by their group-name, GHB, and they are metabolically linked. GHB poisoning results in coma and may result in death. The kits are needed to assist emergency room doctors in rapid diagnosis of GHB poisoning, which is very difficult and critical for selection of proper treatment strategy. The method of detection should be quick, qualitative, and specific and measure GHB concentrations above its endogenous levels.

Division of Epidemiology, Services and Prevention Research (DESPR)

A. ***Prevention Research Branch (PRB).*** The Prevention Research Branch (PRB) supports a program of research in drug abuse and drug related HIV prevention to (1) examine the efficacy and effectiveness of new and innovative theory-based prevention approaches for drug abuse, drug-related HIV/AIDS and other associated health risks, (2) determine the cognitive, social, emotional, biological and behavioral processes that account for effectiveness of approaches, (3) clarify factors related to the effective and efficient provision of prevention services, and (4) develop and test methodologies appropriate for studying these complex aspects of prevention science.

Prevention Research. Rigorous scientific prevention research is encouraged to study novel approaches to substance abuse prevention for use at multiple levels of the social environment including: the family, schools, peer groups, community and faith-based organizations, the workplace, health care systems, etc. The purpose of this research is to determine the efficacy and effectiveness of novel program materials, training strategies, and technologies developed to prevent the onset and progression of drug abuse and drug-related HIV/AIDS infection. Materials and technologies may target a single risk-level or may take a comprehensive approach encompassing audiences at the universal, selective, and/or indicated levels. Universal interventions target the general population; selective target subgroups of the population with defined risk factors for substance abuse; indicated interventions target individuals who have detectable signs or symptoms foreshadowing drug abuse and addiction, but who have not met diagnostic criteria. NIDA encourages the development and testing of innovative prevention intervention technologies that are sensitive and relevant to cultural and gender differences.

1. Laboratory studies of the underlying mechanisms and effects of various prevention approaches such as persuasive communication (e.g., mass media and print media) as they are affected by and effect drug related cognition, emotion, motivation and behaviors.
2. Decomposition of prevention programs, practices and strategies to understand components that account for program effectiveness.
3. Research on features of prevention curricula, materials, implementation, approaches, training, technical assistance, and systems integration that contribute to positive outcomes.
4. Training modules and ongoing technical assistance for program implementers of research based substance abuse prevention programming strategies.

5. Prevention intervention dissemination technologies and mechanisms that integrate research with practice; specifically the transfer of drug abuse prevention information to decision-makers, funders, and practitioners.
6. Prevention services research on the organization, financing, management, delivery, and utilization of drug abuse prevention programs.
7. State-of-the-art and practical strategies for the integration of evidence-based prevention approaches into existing prevention service delivery systems.
8. Studies that develop and assess reliability and validity of developmentally appropriate self-report, physiological, and biochemical measures for use in prevention trials in a variety of settings and a variety of audiences.
9. Development of and testing of environmental change strategies for schools, neighborhoods, communities, etc. to use in reducing substance use initiation and/or progression.
10. Development of practical and affordable community tools for: needs and resource assessment, selection of appropriate evidence-based programs and strategies, high-quality implementation of identified programs and strategies, evaluation at community, organization and individual levels, and sustainability.
11. Drug abuse prevention methodological research on promising data collection, data storage, data dissemination, and reporting techniques.
12. Marketing evidence-based prevention interventions for substance abuse and related HIV prevention.
13. Studies applying technologies and strategies that have been developed for use in other disciplines in order to examine the utility of their application for drug abuse prevention, such as virtual reality technologies being used for some clinical conditions (e.g. phobias, eating disorders), and serious video games are being used for some clinical conditions (e.g., cancer patients), but not for drug abuse prevention.
14. Development and testing of innovative drug abuse prevention intervention products, using discoveries from the basic biological (e.g. neurobiological), psychological (e.g. emotional, behavioral, cognitive, and developmental) and social (e.g. social learning, peer network, and communications) sciences.
15. Development and testing of adaptations for efficacious prevention research approaches to make these more appropriate for special populations including racial and ethnic minorities, non-English speaking populations, immigrant populations, rural and migrant populations, low literacy populations, or persons with disabilities.
16. Development of methods, state-of-the-art tools and systems for community coalition-building.
17. Tools to measure intervention costs, cost effectiveness, and net economic benefits.

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B. ***Epidemiology Research Branch (ERB).*** The ERB supports a research program on drug abuse epidemiology that includes (1) studies of trends and patterns of drug abuse and related conditions such as HIV/AIDS in the general population and among subpopulations, (2) studies of causal mechanisms leading to onset, escalation, maintenance, and cessation of drug abuse across stages of human development, (3) studies of person–environment interactions, (4) studies of behavioral and social consequences of drug abuse, (5) bio-

epidemiologic studies including genetic epidemiology studies, (6) methodological studies to improve the design of epidemiologic studies and to develop innovative statistical approaches, including modeling techniques.

1. *Improvement of Reliability and Validity of Reporting of Sensitive Data*. The reliability and validity of self-report of drug use and related behaviors (e.g., HIV risk behavior) is a matter of great concern. Use of new technologies for real time data collection in ecological settings is of great interest because these technologies enable collection of drug consumption data in context. Studies to improve methodologies based on variations of standard survey protocols or computer-assisted self-interview (CASI) and personal interview (CAPI) are also encouraged.

2. *Instrument Development.* Easy-to-use assessment instruments are needed to enhance epidemiology research. Areas of interest include but are not limited to:

    a. *Community Assessment.* The development of community diagnostic instruments for psychometrically sound assessment of community characteristics is essential to improve our understanding of how community factors affect drug abuse and ensuing behavioral and social consequences. Standardized assessments of community characteristics are needed to better understand the full impact of drug use and to develop targeted interventions to specific community needs.

    b. *Assessment of Psychiatric Comorbidity in Community Settings.* Easy to use, reliable, and valid instruments are needed to assess psychiatric comorbidity in different populations of drug abusers, including adolescents and those in community drug abuse treatment settings.

    c. *Assessment Instruments to Measure CNS Function Related to Drug Abuse.* The development of age-appropriate assessment instruments to measure behavioral and cognitive function over the course of development will contribute to our understanding of vulnerability to drug abuse and functional impairment due to drug use.

3. *Development of State-of-the-Art Mechanisms for Epidemiological Research.* The development of state-of-the-art mechanisms to facilitate the use of Geographical Information Systems (GIS) in community epidemiology studies (for example Community Epidemiology Work Groups) and other drug abuse research is if great interest. There is a need for enhanced software and hardware for GIS interfaces, database management, visualization, and innovative spatial analysis capabilities. The role of GIS in public health management and practice continues to evolve. Application of this technology is an important step towards better understanding drug abuse issues and their inherent complexities. The ability to evaluate geospatial information provides a unique perspective of public health issues such as emerging and shifting epidemics, the utilization of treatment services, and rapid assessment of the impact of incidents ranging from natural disasters to bioterrorism. When used alongside more traditional epidemiological techniques, GIS provides epidemiologists the ability to address new questions, refine, or enhance existing analyses.

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C. ***Services Research Branch (SRB).*** The SRB supports a program of research on the effectiveness of drug abuse treatment with a focus on the quality, cost, access to, and cost-effectiveness of care for drug abuse dependence disorders. Primary research foci include: (a) the effectiveness and cost-benefits and cost-effectiveness of drug abuse treatment, (b) factors affecting treatment access, utilization, and health and behavioral outcomes for

defined populations, (c) the effects of organization, financing, and management of services on treatment outcomes, (d) drug abuse service delivery systems and models, such as continuity of care, stages of change, or service linkage and integration models, and (e) drug abuse treatment services for HIV seropositive patients and for those at risk of infection.

1. *Drug Abuse Treatment Economic Research*. This initiative will support research to design and develop data systems for financial management and economic analysis of treatment programs and larger systems in new healthcare settings and managed care networks. Managerial decision-making requires the implementation of sophisticated data systems to facilitate routine budgeting processes, allocation of resources, performance measurement, and pricing decisions. The focus is on the needs of managers within the organization and managers outside of the organization. Data system development must be based on standard cost behavior and profit analysis. Data systems must be designed with correct cost concepts (accounting and economic) in order to permit cost and pricing decisions to be developed for new treatment technologies and management of ongoing systems. In research settings, such an initiative is vital for the assessment of new technologies developed for transfer to practice.

2. *Determining the Costs of Implementing Evidence-Based Practices (EBPs) and Other Technologies in Drug Abuse Treatment.* Research shows that new technologies or evidence-based practices (EBPs) can improve drug treatment outcomes, and it has been asserted that large-scale drug abuse treatment improvement requires systematic implementation of proven practices, processes, and technologies. Often, however, new drug treatment approaches are not adopted or sustained in usual practice, even in programs that served as settings for research showing their effectiveness. This may be due in part to a poor understanding of the initial or ongoing costs entailed by new practices, processes, or technologies (hereafter referred to as technologies). Methods and tools need to be developed and tested to help drug abuse treatment service providers and payers arrive at realistic estimates of the costs of implementing and sustaining new technologies in usual practice settings. With regard to new technologies, implementing is defined as an ongoing process of selecting, adopting, and adapting these new technologies into ongoing treatment, particularly with consideration for the local setting, population and available resources. Sustaining is defined as an ongoing process of providing needed resources (such as staffing, training, and equipment), maintaining the quality of the new technology through evaluation, monitoring, and improvement, and determining its ongoing utility compared to alternatives. The tools and methodologies should be able to identify and estimate costs separately for implementing and for sustaining new technologies, and should consider both clinical and administrative technology. At a minimum, domains in which costs should be estimated include assessment of programmatic need, appropriateness, and value; staffing qualifications (salary and competencies); training, support, equipment, and other infrastructure requirements; information / data requirements; quality monitoring and improvement; and evaluation of outcomes.

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3. *Personnel Selection Technology Research for Drug Abuse Treatment Clinics*. Research is showing that employee turnover is a substantial problem among substance abuse treatment services providers. Applications supporting innovative research that develops and validates generic staff selection systems which could be adopted and tailored for use by drug abuse treatment clinics are welcome. Like many small businesses, drug abuse treatment clinics have problems attracting and retaining qualified personnel. Also like many small businesses, treatment clinics have limited resources to apply to the

recruiting, screening, and hiring of new and replacement personnel. Research has shown that the application of standardized screening and selection methods designed to maximize person-job fit can cost-effectively reduce staff turnover. Systematic methods such as background inventories, protocol-driven interviews, aptitude tests, and credit checks have demonstrated validity for improving person-job fit. Examples of possible projects might include development of easy-to-understand guidance about legal considerations in hiring practices, software that transform job task analysis into selection criteria, interview protocols to standardize applicant screening, tolls to help improve recruitment, and/or self-paced training for hiring officials or interview panels to improve screening reliability.

4. *Customer Retention Technology*. Premature disengagement from drug abuse treatment participation is a common problem and ranges from approximately 30 to 60% based upon the clinic and modality studied. Past research has very frequently attributed dropping out of treatment to participant characteristics (e.g., motivation, addiction severity, comorbidity) and/or environmental factors (e.g., social pressures, unemployment, homelessness). Seldom has the dropout problem been studied in the context of customer satisfaction. That is, there is little research looking at the causes of dropping out of treatment attributable to organizational factors (e.g., policies, practices, context) that influence participant withdrawal decisions. Needed are tools and systems for assessing and surveying drug abuse treatment program participant perceptions and satisfaction levels, summarizing and report participant assessments, interpreting results, and adjusting policies and practices to improve satisfaction and participant retention in treatment.

5. *Effective Management and Operation of Drug Abuse Treatment Services Delivery*. The bulk of drug abuse treatment is conducted in small clinical settings with therapeutic staffs of less than a dozen people. Small clinics lack resources to help improve efficiency and effectiveness in both business and therapeutic practices. Areas that may be of interest to small businesses include, but are not limited to:

    a. Computer-based leader/manager self assessment tools: On-line and other types of tools to help those supervising the delivery of drug abuse treatment services to gain insights about personal strengths and weaknesses, and to help guide them to improved leadership and management practices.

    b. Organizational change tools: Handbooks describing step-by-step way to introduce more efficient business practices such as quality management/monitoring, creating empowered work teams, formalized goal setting, improved customer relations, forming organization linkages, and adopting new fiscal and resource management techniques.

    c. Organizational change tools: Handbooks describing step-by-step ways to introduce more efficient or effective therapeutic practices such as, adding pharmacotherapy in a previously drug-free clinic, adopting new medical/pharmacotherapy or behavioral interventions, and adopting new approaches to clinical collaboration and/or case management.

6. *Assessment Tools for Quantifying and Organizational Culture that Promotes and Sustains a Drug-Free Workforce.* Though drug-free workplace programs are ubiquitous in large businesses, small businesses often lack the staff and resources to create effective drug-free programs because they may involve in-house or contract experts to educate, train, monitor, and enforce policies and practices that will sustain a healthy workforce and a safe and healthy workplace. Though there are numerous model drug-free workplace policies and programs provided free by federal, state, and local governments as well as nongovernmental organizations, many fail to provide management with affordable or free, easy-to-use tools to assess the baseline of their

organizations' culture for drug abuse intolerance, and to monitor progress in building a drug-free organizational culture. Research shows that individual employees and organizations vary in their support for a drug-free workplace. Surveys indicate that coworker tolerance for illicit drug use varies by the type of drug, the type of industry, and the work role of the respondents. A drug-free culture creates commonly-held attitudes, beliefs and practices among employees that are socially reinforced. Once established, the need for costly external incentives and other measures abates as coworkers socialize new incumbents and enforce behavior promoting abstinence. Tools and methodologies need to be developed to a) assess an organization's baseline culture for drug abuse intolerance both on and off the job, b) identify policies and practices that undermine a drug-free culture, c) enable the identification of programs, policies, and practices capable of helping the workforce develop/strengthen an organizational culture of intolerance for drug use, and d) estimate the impact on the organization's quality of work-life, job safety, individual and group performance and productivity, and the profitability of the organization itself. Included would be inexpensive and easy to use tools for monitoring workforce behavior change, and changes in the impact on the organization (as outlined in "d").

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7. *Web-Based Technologies: Transporting Services Research to Practice*. This initiative will support the development and testing of the effectiveness of web-based technologies that facilitate the translation of drug abuse prevention and treatment services research into practice. The ultimate goal is the delivery of efficacious, low-cost interventions to the greatest number of individuals in community settings. Delivery of evidence-based services in community settings often is hampered by lack of state-of-the-art information about the contents of efficacious interventions, the organizational structures and processes that make effective implementation possible, and available training and technical assistance. Applications may include, but are not limited to, the development and testing of new and innovative Internet-based systems that provide practitioners with (a) current information on evidence-based treatments with the greatest promise for defined populations of drug abusers; (b) assistance in translating clinical trials data into clinically useful information; (c) information and training on how to effectively organize, manage, and deliver evidence-based prevention and treatment services; (d) strategies for organizational change and capacity building; and (e) access to training and technical assistance on the adoption of new prevention and treatment interventions.

8. *New Technologies for Screening, Assessing, and Preventing Problem Drug Use and HIV, Matching Patients with Appropriate Treatment Services.* Increased understanding of the complexities of problem drug use and HIV risk behaviors has sparked growing interest in and increased need for new user-friendly technologies to assist in the screening, assessment, and prevention of drug abuse and HIV, and in the matching of patients with appropriate treatment services. New technologies, including CD-ROM, hand-held, Internet, videotape, videodisc, and other electronic means have great potential for helping treatment providers in specialty and non-specialty care settings including primary care contexts to (a) screen for problem drug use and associated health problems and risk behaviors, including HIV, (b) assess the nature and degree of drug use and HIV risk behaviors, (c) embed items for screening or assessing problem drug use within existing clinical tools, (d) deliver appropriate prevention interventions, and (e) identify appropriate types and levels of treatment services for patients based on their individual treatment needs. These new technologies potentially can provide a more cost effective way of identifying problem drug use, HIV risk behaviors and infection, and

associated health problems in a variety of health care settings, speeding the assessment and treatment process, and improving treatment placement decisions.

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9. *Reintegration of Criminal Offenders into the Community.* Many offenders enter the criminal justice system with drug abuse problems and related health issues. In addition to addressing these health care issues within the prison walls, treatment programs are increasingly called upon to help offenders successfully reintegrate into the community following incarceration. This often means helping offenders to manage their recovery through monitoring, linkage with continuing care services, development of social support networks, and education of friends and family members about the nature of drug abuse and the challenges facing the offender upon release from prison. It is estimated that over the next several years, more than 600,000 criminal justice offenders, many of whom have drug abuse problems, per year will be released to return to their communities. New technologies are needed to help treatment providers in the criminal justice system and in the community coordinate efforts to effectively (a) monitor offenders' recovery once they have been released into the community, (b) prevent relapse, (c) identify relapse early and efficiently re-engage released offenders in appropriate treatment, (d) link released offenders with continuing care services in the community, (e) develop social support networks for recently released offenders in recovery, and (e) educate offenders' family members so that they can more effectively support offenders in recovery once they have been released from prison.

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10. *Technologies to Support Quality Improvement in Addiction Treatment Systems.* New technologies to support quality improvement in community-based, addiction treatment provider systems are needed. Quality improvement methods, although well established in business and healthcare management, are underutilized in addiction treatment. Addiction treatment systems have limited resources for initiating, developing, implementing, and sustaining quality improvement practices. Most community-based provider systems have limited capacity to capture and integrate information about (a) the nature and extent of community needs and resources; (b) organizational and management processes to facilitate adoption, adaptation, implementation, and sustained use of science-based innovations; (c) implementation costs for new service innovations; (d) client satisfaction; and (e) quality of care. Centralized, automated and cost-efficient technological tools for these purposes could help provider systems improve the quality and efficiency of their treatment services, meet accreditation requirements, and reduce operating costs.

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11. *Electronic Drug Abuse Treatment Referral Systems for Physicians.* Research shows that primary care physicians often do not screen for drug abuse disorders. While this may be related to stigma attached to illicit drug use or to a lack of adequate health insurance, it may also be due to the lack of an adequate referral system that primary care physicians can use for the patients they identify as having a potential drug problem. The lack of a referral system places a greater burden on the physician to secure treatment resources for the patient, and also places the physician at greater risk if no

appropriate treatment can be found. A practical and usable electronic drug abuse treatment referral system needs to be developed and tested for use by physicians in primary care settings, including doctor's offices. To be effective and useful, the system needs to be targeted at local needs, for example by taking into account local private insurance coverage and the types of insurance accepted by local treatment providers. It should also include an actively-maintained database of local providers, with information on insurance carrier, geographic "catchment" area of treatment providers, types of substance disorders treated, types of co-occurring disorders (mental disorders, etc.) treated, gender, age, other pertinent treatment factors needed by primary care physicians to make appropriate referrals. The system should be designed to be reliable and efficient, allowing for appointment scheduling or other needed arrangements to ensure a successful referral. Feasibility and cost-efficiency should be carefully considered.

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Center for the Clinical Trials Network

The mission of the Clinical Trials Network (CTN) is to improve the quality of drug abuse treatment throughout the country using science as the vehicle. The CTN provides an enterprise in which the National Institute on Drug Abuse, treatment researchers, and community-based service providers cooperatively develop, validate, refine, and deliver new treatment options to patients in community-level clinical practice. This unique partnership between community treatment providers and academic research leaders aims to achieve the following objectives:

- Conducting studies of behavioral, pharmacological, and integrated behavioral and pharmacological treatment interventions of therapeutic effect in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations; and

- Ensuring the transfer of research results to physicians, clinicians, providers, and patients.

Materials and processes that facilitate clinical trials in community practice settings are particularly needed in this program. Areas of research include but are not limited to:

- Projects that would simplify, automate, standardize, or reduce the cost of administration of clinical research instruments used in CTN trials

- Projects that would reduce error rates in completing assessment or clinical instruments and in transmitting data to data management entities

- Projects to develop instruments that measure factors relevant and important to the conduct of addictions research, such as: the extent of craving and/or of withdrawal, the risk of addiction to a particular substance, the therapeutic alliance between patient and therapist, perceived satisfaction with health care, probabilities of a pain management patient developing dependence/abuse on pain medications, and probability of successfully completing detoxification

- Projects to develop instruments that measure and predict HIV risk behaviors

- Projects that develop and evaluate innovative diagnostic drug screening tests for drug abuse, such as oral swabs

- Projects that develop and evaluate the use of gene chip technology for drug abuse risk factors

Specific projects could include:

1. *Development of Innovative Techniques/Tools for the Screening, Recruitment, and Follow-up of Participants in Drug Abuse Trials.* Screening and recruitment of participants for multi-center clinical trials pose a number of problems. Tracking devices/programs are needed to document and manage a patient's interaction throughout a clinical trial. This would include screening tools, recruitment strategies that could be followed, and steps to increase and document follow-up practices. Validated materials/tools applicable to diverse populations for use in education and counseling of potential participants are needed. These tools would be applicable across trials and would provide a strategy for management to improve clinical trial performance. These recruitment concerns are particularly relevant for community practices, which often do not have the resources of larger hospitals or academic institutions. Both the participants and the research clinicians administering the trial would benefit from this product. Approaches are needed to develop innovative techniques and/or tools for the screening, recruitment and follow-up of clinical trial participants in drug abuse trials. These tools or techniques can be from the standpoint of clinicians who are running the clinical trials, to patients who are participants in the drug abuse trials. Tools can include software for following up on participants, reminder tools for clinical trial participants, technological devices for clinician or patient use. The ultimate goal is to make the trial management more efficient and effective.

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2. *Development of Practical Training Materials for Evidence-Based Treatment.* States have initiated the requirement that community treatment programs provide evidence-based treatment or risk losing their public funding if they don't comply. The onus is on the publicly funded program to provide their staff with training in evidence-based treatment modalities. Current staff training opportunities in evidence-based treatments are expensive and frequently require repetition because of high rates of staff turnover. The level of staff training and education varies across agencies. Certification in evidence-based treatment has not been standardized. Externally presented training is not timely or efficient. Computers with Internet capabilities are not always available for staff learning opportunities. It is important to offer alternatives to the delivery of training that are easy for staff to access and that meet requirements to provide evidence-based treatment. There is a need for practical, non-computer and interactive, self-administered computer versions for training counseling staff in evidence-based drug abuse treatments. Such programs should include competency testing to meet local and state requirements for certification, such as, motivational incentives, motivational interviewing, cognitive-behavior therapy, and other proved therapies.

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3. *Innovative Diagnostic Drug Screening Tests for Drug of Abuse.* Drug screening and the detection of drug use/abuse prior to and during treatment episodes are an important factor in defining treatment progress and outcome. Rapid results from the tests are important in addressing a patient's behavior in a clinically effective manner. The time and personnel resources required to perform this function are costly and cumbersome. Current urine tests often require visual corroboration from a staff member of the same gender as the participant in order to ensure that the urine samples are legitimate. This takes staff time away from

other duties and requires a separate facility for patients to give urine samples. Clinics have to schedule enough male and female employees to observe these tests. Effective and cost-efficient approaches to testing using oral swabs, patches, and/or other methods would be welcomed by the treatment clinics. To date the newer technologies are not cost effective for most programs. Additionally, immediate or less than 24-hour results are not available as is true with most urine screens. Innovative and inexpensive technologies and/or products are needed that provide for on-site, rapid drug screening, are minimally invasive for the patient, and are gender neutral for the program staff.

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4. *Development of Drug Use Patch.* It is difficult to accurately track a patient's drug use when they are outpatients in a program or study. Relying on a weekly or monthly urine test is not always reliable. History indicates that patients are more likely to abstain from illegal drug use when their behavior is observed. This initiative is for the development of a cost effective and tamper proof patch to detect drug use that can be worn by patients. The patch should be one that can be worn for 1-2 weeks. After it is applied and worn for a length of time, the patient would come into the clinic, and the patch would be and analyzed for drug use. The patch should be contain chemical profiles for at least 4 major categories of illicit drugs and be easily worn for up to a month and non-irritating to the skin.

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5. *Internet Based Program for Patient Referral.* Electronic health information is widely used by patients and families to seek treatment options. For drug abuse, development and testing of an internet-based program for individuals to assess their own levels of drug use/misuse/addiction using up-to-date measurement tools would be useful. The program should then provide contact and descriptive information of treatment options appropriate for the individual's level of abuse and provide contact and descriptive information for treatment settings available in the individual's specific location. The system should incorporate and integrate modern healthcare informatics technology into conventional evidence based behavior prevention/intervention medicine.

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6. *Development of eHealth Tools.* eHealth, the healthcare practice supported by electronic processes and communication, offers the potential to increase quality, enhance reach, lower cost, resolve time/distance concerns, and customize patient care. Information technology can be implemented to support a broad array of applications. We are looking for novel, unique, state-of-the-art eHealth tools (software and hardware) that can be implemented to promote the efficacy and safety of clinical trials in the area of substance abuse (e.g., the development of a tool that could be used to change behavior and reduce the drug addiction). Security and privacy should be considered in the application of these tools to protect patients.

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7. *Development of Instruments To Assess Co-morbidities.* Drug and alcohol treatment centers lack a brief assessment instrument to screen their patients for mental health disorders. There are diagnostic instruments available; however, they require specialized training and can be time consuming to administer. For this reason and others, co-morbid conditions such as depression, ADHD or PTSD often go undiagnosed and untreated in this population. If clinicians had a proper instrument to screen these patients, they could then refer them for further evaluation. This initiative is for the development and validation of an instrument to be used in community practices to screen for mental health disorders when patients present themselves for drug and/or alcohol treatment. The instrument should be easy to use either by the clinician (as an interview) or by the patient (as a self assessment) and could be either in paper format or computerized.

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8. *Development of Practical Training Programs for Addressing Learning Disabilities in Drug Abusers in Treatment. Development of Practical Training Programs for Addressing Learning Disabilities in Drug Abusers in Treatment.* Compared to the general population, individuals in drug abuse treatment are much more likely to have a learning disability. Because many commonly employed drug abuse treatment approaches are dependent on patients/clients' ability to understand and apply new information, even relatively minor learning impairments may limit the potential benefits of these interventions and adversely affect drug abusers' treatment outcomes. For an individual patient/client's treatment regimen to have an optimal chance of success, it should be tailored to address any co-occurring disorders, including learning disabilities, that may be present. There is a need for training programs that provide clinicians with guidance and practical tools for shaping their treatment approaches in response to learning disabled drug abusers' individual needs. These programs may incorporate training regarding screening for and assessment of learning disabilities and/or provide links to appropriate resources that address these topics. Developers should also consider utilizing user-friendly and engaging training strategies (e.g., web-based training, interactive learning, case studies) where appropriate.

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Division of Pharmacotherapies & Medical Consequences of Drug Abuse

The NIDA Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA) supports research aimed at the development and testing of pharmacological and behavioral treatments for drug abuse and addiction. This includes the identification, evaluation, development, approvability, and efficacy testing of new and improved pharmacotherapeutic agents, as well as the testing of marketed medications, and of behavioral treatments used alone or integrated with medications.

A. ***Chemistry and Pharmaceutics Branch (CPB).*** The CPB supports research in the design (including molecular modeling and structure-activity relationship studies) and synthesis of novel compounds, formulation development, bioanalytical methods development, and pharmacokinetics/ pharmacodynamics aimed at the discovery and development of new medications for treating drug addiction. Areas that may be of interest to small businesses include, but are not limited to *research related to the design and development of new compounds and improved drug products (drug delivery) for the treatment of drug addiction*:

1. Synthesis (either using traditional or combinatorial techniques) or discovery (natural products) of new chemical compounds that would have potential as treatment agents for the medical management of stimulant (e.g., cocaine, methamphetamine, or nicotine) addiction. Consideration should be given to the design of partial agonists or pure antagonists that diminish the reinforcing effects of stimulants, as well as full agonists that could function to normalize physiological activity following discontinuation of stimulant use.

   Compounds of interest include those that are designed to affect dopaminergic (i.e., D1 agonists, D3 agonists and D3 antagonists) activity, CRF antagonists, compounds affecting glutamate activity, GABAergic activity, small molecule neuropeptide antagonists and compounds acting through other mechanisms for which justification has been supplied.

2. Synthesis (either using traditional or combinatorial techniques) of new chemical compounds that would have potential as treatment agents for the medical management of cannabinoid abuse.

3. Development of new immunotherapeutic treatments that would have the potential as treatment agents for stimulant, opioid or cannabinoid abuse.

4. Development of heroin/morphine-protein conjugates (heroin/morphine conjugate vaccines) for the treatment of heroin/opiate addiction.

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5. Development of new approaches for the administration of potential addiction treatment drugs with poor bioavailability.

6. Development of controlled release dosage forms for addiction treatment medications in order to maintain therapeutic drug levels for extended periods of time to alleviate compliance problems associated with addiction treatment.

7. Development of novel dosage forms or chemical/pharmaceutical approaches that eliminate or significantly reduce the abuse potential of prescription drugs/drug products.

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B. ***Medications Discovery and Toxicology Branch (MDTB).*** The MDTB supports research on the development of preclinical behavioral models (e.g., of craving, drug-seeking behavior, dependence, or relapse), biochemical assays, gene expressional assays and electrophysiological methods to identify and characterize new medications to treat substance abuse, as well as pharmacological screening of novel compounds to identify potential drug abuse medications. The Branch also supports research on toxicity studies of potential medications for the treatment of substance abuse, and interactions of potential treatment medications with abused substances. Areas that may be of interest to small businesses include, but are not limited to *development of new methods for discovery of medications useful in treating drug addiction*. Of special interest would be the development of new animal models of addiction, incorporating established drug self-administration techniques that show increased relevance to the clinical setting. Development of relevant biochemical or electrophysiological screening methods is also encouraged.

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C. ***Medications Research Grants Branch (MRGB).*** The MRGB supports investigations of the use of therapeutic agents (including vaccines and monoclonal antibodies) for the treatment of substance related disorders, with the aim of assisting in reducing drug use, becoming drug free, prolonging abstinence, decreasing associated psychosocial, medical or legal problems, or surviving drug overdose. In general, therapeutic agents are expected to be investigated using a platform of appropriate psychosocial interventions. The program funds extramural grants in the following areas:

- Clinical trials to test the safety, find the optimal dose, and/or obtain preliminary efficacy data for new agents or new indications of marketed medications. This phase includes interaction studies to test the safety of the agent when used in combination with drugs of abuse.

- Clinical trials to assess the efficacy of new agents or marketed medications for the treatment of substance related disorders. In general, these types of trials use a randomized double blind placebo controlled design.

- Clinical studies of the efficacy of medications for the treatment of the comorbidity of substance related disorders (e.g., alcohol and cocaine dependence) or the comorbidity of these disorders with other medical or psychiatric conditions.

- Clinical evaluation of the efficacy of medications for the treatment of substance related disorders in specific groups of the population. For example, adolescents, the elderly, women of childbearing age, pregnant and/or postpartum women, as well as racial and ethnic minorities.

- Evaluation of biological and/or psychosocial factors that may affect the outcome of the pharmacotherapy of substance related disorders.

Specific areas that may be of interest to small businesses include, but are not limited to:

1. *Pharmacogenetics and Substance Use Disorders.* The emergence of new genetic techniques may allow the use of genetic information to improve the safety and efficacy of treatments. The field of pharmacogenetics focuses on the genetic determinants of response to medications and other therapies in humans and animals. The goal is to discover novel single nucleotide polymorphisms (SNPs) and test their relevance to the underlying genetic differences that determine the safety and efficacy of medications for the treatment of SUD. It includes the study of genes encoding drug metabolizing enzymes, transporters, receptors and other drug targets, polygenic determinants of drug disposition and effects in humans, the role of genes in the clinical response to and medical safety of medications, and application of genetic information to disease prevention and to optimize treatments in humans. It also includes novel methods for phenotyping the diagnosis, safety and treatment outcome of SUD. Ultimately, it is expected that pharmacogenetics research will help clinicians to individualize the treatment of their patients based on their genetic information. Research is needed to study the genetic factors that may be associated with drug abuse treatment safety and outcome.

2. *Medications Development for the Treatment of Drug Abuse in Adolescents.* Drug abuse among adolescents is a significant and growing public health concern. It is known that the pharmacokinetics and pharmacodynamics of some medications are different in adolescents. Therefore, adolescents may present overdoses, underdoses or lack of efficacy, or different safety profiles when administered medications at the doses studied only in adults. Unfortunately, little is known about the safety and efficacy of medications

for the treatment of drug abusing adolescents because most of the drug abuse medication research has focused on adults. Research is needed to test medications for the treatment of nicotine and drug abuse in adolescents.

3. *Medications for the Treatment of Comorbid Medical or Mental Disorders and Drug Abuse.* Co-morbid medical and psychiatric conditions are frequently found among substance abusing patients. Co-occurring mental disorders, such as depression, post-traumatic stress disorder, and anxiety disorder, and medical conditions such as hepatitis C, AIDS related disorders, and pain, are common among substance abusing patients. Unfortunately, there are presently no commonly prescribed safe and effective medications for the treatment of substance abusing patients with other co-morbid medical and psychiatric conditions. Research is needed to study the safety and therapeutic profiles of medications for treatment of substance abuse in patients with other comorbidities. There is also a need to study the effects of medications for the treatment of substance use disorders in patients taking medications for other comorbid conditions and the necessary dose adjustments.

4. *Development of Software for Data Management of Medical Safety Data from Clinical Trials.* Recent policies for the protection of human subjects participating in clinical trials are requiring increasing levels of medical safety monitoring. Currently, adverse event and serious adverse event data management (collection, storing, analysis, and reporting) is heterogeneous. Different investigators use different nomenclatures, definitions, timeframes, data collection instruments, and data analysis and reporting methods. This heterogeneous and often inadequate data system limits the interpretation of safety results and the ability to make sound decisions about the safety (and often the efficacy) of clinical trials. In some instances, external reviewers may misinterpret the reported signs or symptoms and may provide wrong recommendations. Furthermore, inadequate safety data does not allow comparing the adverse events and serious adverse events results across multiple clinical trials, which hinders the scientific progress, and increases costs. The purpose of this initiative is to stimulate research on innovative medical safety data management tools for clinical trials testing interventions for drug addiction, while guaranteeing the privacy and confidentiality of study participants. Appropriate management of medical safety data will enhance the protection of human subjects, optimize the reviews by IRBs, DSMBs, funding and regulatory agencies, promote the trust of participants and the community in clinical trials, enhance scientific progress, and lower research costs.

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5. *Medications for the Treatment of Pregnant and Post-Partum Drug Abusing Women and Their Children.* Little is known about the safety and efficacy of medications for the treatment of substance abusing pregnant women and their children. There is a need for safe and effective medications for the treatment of nicotine and drug abuse/dependence among pregnant and post-partum women and the effect of these medications on their children. Research is also needed to study the effects on the newborn of the medications taken by the mother and medications for treatment of children born to substance abusing mothers who may present drug withdrawal and other symptoms.

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6. *Immunotherapy for Addiction Treatment.* The MRGB supports research on the advanced stage development of monoclonal antibodies and vaccines for the treatment

of drug and nicotine addiction and/or overdose. Monoclonal antibodies have been reported as possible treatment agents through passive immunization for PCP, methamphetamine, MDMA, and cocaine overdose and may also serve to minimize abuse and prevent relapse. New vaccines are being developed as therapies for drug or nicotine cessation and relapse prevention. New technologies, such as the production of antibodies in plants, are emerging as cost-effective and efficient ways for the large scale manufacture of immunotherapy agents, represent another facet of this area for development.

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Division of Clinical Neuroscience and Behavioral Research (DCNBR)

A. ***Behavioral and Integrative Treatment Branch.*** The Behavioral and Integrative Treatment Branch is interested in research on behavioral and integrative treatments for drug abuse and addiction. The term "behavioral treatments" is used in a broad sense and includes various forms of psychotherapy, behavior therapy, cognitive therapy, family therapy, couples and marital therapy, group therapy, skills training, meditation, guided imagery, counseling, and rehabilitative therapies. The term, “Integrative treatments” refers to treatments that combine behavioral interventions with other treatments, including other behavioral therapies, medications, and/or complementary/alternative therapies. Behavioral and integrative treatment research has been conceptualized to consist of three stages. Stage I, or early treatment development, involves research on the development, refinement, and pilot testing of behavioral and integrative interventions. Stage I may include translational research that incorporates concepts, methods or findings from other disciplines (e.g., neuroscience, cognitive science, etc.) into the development of behavioral and integrative treatments. Stage I may also include research to develop or adapt treatments to become more “community-friendly.” Stage II includes testing treatments that show promise and testing the “dose-response” of treatments. Stage III is research aimed at determining if and how efficacious behavioral treatments may be transported to community settings. Stage III may include studies that test treatments in community settings, with community therapists. Stage III may also include studies that develop or test methods of training treatment providers to administer treatments. Determination of mechanism of action of treatment is relevant to all three stages. Specific areas of interest include:

1. *Translation from Basic Behavioral or Cognitive Science.* “Stage I” research on the development of behavioral therapies or components of such therapies that are based on developments and findings from the basic behavioral or cognitive sciences.

2. *Translation of Cognitive, Affective and Social Neuroscience Findings Towards Development of Behavioral Treatments.* “Stage I” research on the development of behavioral treatments or components of such therapies that are based on developments and findings from cognitive, affective, or social neuroscience.

3. *Treatment of Sleep Disorders for Individuals in Drug Abuse Treatment.* Recent research on sleep has shed new light on its importance to psychological and physical health. Sleep deprivation has been linked with impaired cognitive performance, negative mood, and even decreased immune function. Drug abusers often cite insomnia as reason for relapse, and may use drugs to modulate their sleep/waking cycles. However, the treatment of sleep disorders has not been a primary focus of drug abuse treatment research. The development and testing of sleep hygiene interventions, alone or in combination with behavioral interventions, for use in conjunction with drug abuse treatment, as a means of improving treatment for drug abuse is needed.

Developmentally and age appropriate, as well as gender sensitive treatment of sleep disorders could impact on the development of more effective treatment interventions.

4. *Modifying Efficacious Behavioral Treatments to be Community Friendly*. Several behavioral interventions have been found to be efficacious for the treatment of drug addiction. However, there are barriers to implementation of behavioral treatments in community-based settings. Community settings that treat drug addicted individuals are reluctant or unwilling to adopt these interventions for a variety of reasons. Reasons that scientifically-based behavioral treatments are not accepted by community providers could include the excessive cost of implementation, the length of time for administration of treatment, inadequate training available for therapists and counselors, treatments not shown to be generalizable for different patient populations or for polydrug abusing populations, etc. Research aimed at modifying efficacious behavioral treatments to make them more acceptable to community settings is needed. Settings might include, drug abuse treatment facilities, primary care, managed care, and the criminal and juvenile justice system. Examples of possible studies are those that are designed to reduce the cost of treatments, reduce the time of administration of treatments, aid in training of therapists, counselors and nurses, adapt individual therapies for group situations, etc.

5. *Improving Adherence to Medications and Treatment for Drug Abusers with HIV/AIDS.* The introduction of highly active antiretroviral therapy (HAART) has significantly changed HIV/AIDS clinical care. There is a need for research related to the development and testing of new and improved behavioral interventions(alone, and in combination with pharmacological treatments for drug addiction), in order to facilitate better adherence to antiviral regimens among drug abusers with HIV infection, including HIV positive drug abusers with comorbid medical illnesses and/or psychiatric disorders. There is also a need to develop and test adherence interventions administered or assisted by technological devices such as computers, the internet, expert system models, telephone pagers, or hand-held computers.

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6. *Behavioral Strategies for Increasing Compliance in Taking Treatment Medication*. Research to develop and to evaluate strategies to induce recovering addicts to take medication for a prolonged time, especially antagonists such as Naltrexone; to induce HIV infected drug users to comply with medical treatments (HAART) in drug abuse treatment settings; or to adapt existing behavioral strategies to increase patient compliance and cooperation in long-term treatment for drug abuse or for diseases associated with drug abuse such as tuberculosis or hepatitis. An important consideration should be cost and practicality of use in actual clinical practice or in an aftercare program. The product of such research might be a manual, which describes the behavioral strategy, and its implementation by treatment staff or scientific data regarding evaluation.

7. *Integration of Behavioral Treatments and Pharmacotherapies*. Development of integrated behavioral treatments and pharmacotherapies may enhance the efficacy of both types of therapeutic interventions. For instance, the maintenance and detoxification of heroin addicts could perhaps be optimized by the integration of distinctive behavioral treatments devised specifically for opioid agonists, antagonists or partial agonists determined by the heterogeneity of the subgroup of addicts and the pharmacological differences of the medications. Integration of medications and behavioral treatments could possibly enhance compliance with medication regimens, *increase* retention

allowing pharmacological effects to occur and prevent relapse to drug abuse and addiction.

8. *Treatment Modules for Specific Problems or Populations.* Discrete therapy components that address specific problems common among drug addicted individuals and that can be implemented in conjunction with other therapeutic services. For example, an investigator may wish to develop a four session, highly focused, job seeking skills module that can be easily implemented by a wide range of practitioners to effectively increase appropriate job seeking behavior. Other examples include, but are not limited to, modules to engage ambivalent drug dependent individuals in treatment, modules to increase assertiveness in female drug addicts who feel pressured by others to use drugs, or to incorporate effective HIV risk reduction techniques.

9. *Behavioral Treatment Research for Drug Abuse and Addiction in Primary Care*. Recent research has shown that physicians and other clinicians often fail to recognize drug abuse or addiction among their primary care patients. In addition, a significant number of these clinicians reported that they did not know how to intervene with their patients if drug abuse or addiction was suspected. Drug abuse related illnesses and morbidity often occur in adults and may have begun in adolescence. However, very little research has been done to develop or test behavioral treatment approaches or combined pharmacological and behavioral treatments for drug abuse and addiction in primary care settings. The objectives of this initiative are to encourage research on the development and testing of innovative brief behavioral treatment approaches, alone or in combination with pharmacological treatments that may be used in various primary care patient populations and primary care settings. Other goals of this research initiative are to encourage additional research on the development and evaluation of culturally sensitive screening and assessment instruments for use in primary care; and to encourage research on the transportability of efficacious behavioral treatments to primary care settings, as well as research on science-based training approaches for changing primary care clinicians' behaviors regarding their recognition and intervention with drug abusing or addicted patients. While motivational enhancement approaches for some drug abusing populations have been found to be effective, this behavioral approach has not been widely used in primary care.

10. *Using Telemedicine to Disseminate Drug Addiction Research Findings to Primary Health Care Providers*. Telemedicine programs are being used in urban medical centers to rapidly disseminate science-based information on new medical treatments. In addition, approximately one-third of the rural hospitals are now using telemedicine to improve patient care. Health care professionals need science-based information on drug abuse prevention and treatment. Research to develop and evaluate telemedicine programs to transport science-based information on drug addiction to the primary health care community is encouraged.

11. *Developing, Evaluating, and Transporting Culturally Sensitive Behavioral Treatments for Racial and Ethnic Minorities*. Minority populations are disproportionately affected by the consequences of drug abuse. Research to develop and evaluate behavioral treatments that are culturally sensitive and relevant for diverse racial and ethnic minority populations is encouraged. This may include studies of behavioral treatments, alone or in combination with pharmacological treatment, or studies of behavioral strategies for increasing adherence to taking medications. In the development and evaluation of the behavioral treatment, attention needs to be directed at examining medical, social, and cultural factors that may influence adherence to the behavioral treatment approach and treatment outcome. Also, little is known about the transportability of efficacious behavioral treatments for minority populations. Research is needed on how to transport science-based treatments to various racial/ethnic populations.

12. *Treatment for Emerging or Specific Populations.* Therapies designed to intervene with understudied populations including users of drugs such as methamphetamine, MDMA and other club drugs, marijuana, inhalants, and prescription opioids and psychostimulants, as well drug abusers with comorbid psychiatric disorders and/or medical illnesses such as HIV/AIDS, hepatitis, etc.

13. *Treatment to Prevent Escalation from Abuse to Dependence.* Therapies for drug abusers who are not yet dependent on drugs to reduce risk of escalation to dependence and therapies for drug abusers who have not considered or claim little interest in seeking treatment for their drug problems. For these populations treatments are needed which interest and engage the potential client and intervene with them. Treatments for participants in their natural environment, such as treatments delivered over the Internet or in neighborhood settings such as churches and recreation centers are desired.

14. *Incorporating Smoking Cessation in Drug Abuse Treatment*. Research is encouraged to develop and test behavioral and combined behavioral and pharmacological treatments for nicotine-addicted individuals who also are addicted to other substances, such as heroin, cocaine, methamphetamines and alcohol. Prevalence of cigarette smoking is extremely high among drug dependent individuals attending drug treatment. Many treatment providers are reluctant to address smoking cessation with clients either because they believe that substance abusers are not interested in quitting or because they fear smoking treatment will have a negative impact on drug abuse treatment outcome. However, studies have shown that many drug abuse clients are interested in quitting smoking and that the concurrent treatment of tobacco dependence and other drug dependencies does not threaten abstinence and might even assist in maintaining it. Research is needed to develop and test smoking cessation treatments that can be incorporated into treatments for illicit drugs of abuse.

15. *Developing Treatments for Smokers with Comorbid Disorders*. Research is encouraged that focuses on the development, refinement, and testing of behavioral treatments for smokers with psychiatric comorbidity, such as depression, schizophrenia, or anxiety disorders. Smoking prevalence is very high in individuals with psychiatric disorders. These populations generally respond poorly to traditional smoking cessation treatments. Research is needed to develop and test innovative behavioral and combined behavioral and pharmacological treatments that address the unique needs of these individuals.

16. *Developing Behavioral Treatments for Cognitively Impaired Drug Abusers.* While there are currently many efficacious interventions available for drug addicted individuals in treatment, more can potentially be done to enhance treatments by addressing cognitive impairments that may accompany chronic drug use and HIV infection. Many commonly utilized drug addiction and HIV-risk reduction interventions assume certain basic cognitive capacities and abilities that may be absent, or impaired, in chronic drug abusers who may also be HIV-positive. For substance abusers to benefit from psychological treatment, they must be capable of attending to and receiving new information, integrating it with existing information stores, and translating this input into more concrete behavioral change. Substance abusers with cognitive limitations, who may not comprehend the interventions, are more likely to drop out of treatment, relapse faster, and have poorer long-term outcomes in comparison to cognitively intact substance abusers. Research is needed to develop, modify, and test "cognitive-friendly" drug dependence treatments that could lead to improved treatment response and outcome.

17. *Tobacco Cessation for Pregnant and Post-Partum Women.* Smoking among pregnant women remains an ongoing public health concern. It is estimated that approximately 20-30% of pregnant women smoke. Maternal smoking during pregnancy has been linked to infant mortality, impaired fetal brain and nervous system development, premature and

complicated births, and low birth-weight babies. For women who do quit during pregnancy, relapse rates vary, but are reported as approximately 25% before delivery, 50% within four months postpartum, and 70-90% by one year postpartum. Children of smokers continue to be at risk for respiratory illness, middle ear infections, impaired lung function, and Sudden Infant Death Syndrome. Sustained tobacco cessation during pregnancy and the postpartum period reduces health risks to both mothers and their babies. Research focused on the development of innovative behavioral and combined behavioral and pharmacological interventions for nicotine-addicted pregnant and postpartum women is encouraged. Interventions may be tailored to sub-populations of pregnant smokers, such as teenage girls, heavy smokers, or ethnic minorities. Examples of other potential studies may include the development of smoking cessation interventions that address co-occurring issues, such as depression or weight-gain, interventions that include partners or support persons, Internet-based interventions or interventions that can be delivered by primary care physicians.

18 *Youth Smoking Cessation.* Smoking related illnesses usually occur in adults. However, tobacco use and nicotine addiction generally begin in childhood or adolescence. Despite health warnings, adolescents continue to initiate smoking at alarming rates and the majority will continue to smoke as adults. Adolescents who begin to smoke, develop nicotine dependence very quickly and exhibit withdrawal symptoms during quit attempts in a similar fashion to adults. Most adolescents who smoke, express a desire to quite. To date, research on smoking cessation for teen smokers has not been particularly fruitful. More research is needed to develop interventions for young smokers. This initiative requests research aimed at the development and testing of smoking cessation treatments tailored to the specific needs of adolescents. Consideration should also be given to gender and ethnicity.

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19. *Development of HIV Risk Reduction Interventions*. Research to develop and evaluate behavioral strategies to reduce HIV risk behaviors in HIV-positive and HIV-negative substance abusing treatment populations. Where appropriate, risk reduction interventions should be adapted to patients' age, gender, cultural background and potential cognitive impairments, and should address compliance with medical regimens. The product of such research might be training, supervision, or educational materials, such as manuals or videotapes that describe the intervention and its implementation by treatment staff.

20. *Woman and Gender Differences in the Provision of Behavioral Treatments, and HIV/AIDS Risk Reduction Approaches*. Develop and evaluate specific behavioral treatment approaches targeting drug-addicted women. This may include behavioral therapies, skills training techniques, counseling strategies, and HIV and other infectious disease behavioral risk reduction strategies. This may also include development and testing of training materials that specifically address women and gender differences in drug addiction treatment to promote effective use of research-based treatment approaches. Training materials may involve treatment manuals, training videos, CD ROM or DVD technologies, Internet or computer based programs to manage aspects of treatment administration, or other innovative educational strategies for health professionals using new technologies.

21. *Interventions to Improve Engagement and Retention in Treatment.* Therapies designed specifically to engage and retain individuals in treatment, especially those at high risk for HIV. An example could be a therapy that is: (1) sensitive to the motivational level of the client; (2) is specifically designed to respond to the needs of the individual, whatever his

or her motivational level might be; and (3) actively works to increase an individual's desire to remain in treatment.

22. *Complementary and Alternative Medicine Therapies (CAM) for Drug Abuse Treatment*. Research is encouraged on complementary and alternative interventions for drug abuse treatment. CAM interventions could be the sole treatment or could be adjunctive strategies to enhance the therapeutic potency of existing drug abuse treatments. An example of an adjunctive CAM intervention might be where the intervention reduces withdrawal symptoms thus enhancing retention in treatment. Included would be interventions that are commonly used in "real world" treatment settings, but whose therapeutic efficacy has not been scientifically demonstrated. Such interventions include acupuncture, bioelectrical stimulation, exercise, biofeedback, meditation, among others. The product of this research might be a manual or video, which illustrates the intervention and how it is implemented by treatment staff.

23. *Development of New or Improved Addiction Assessment Measures and Procedures*. Research directed at the improvement of a currently available measure or the design of a new psychosocial, social or environmental measure appropriate for use in the clinical assessment of substance abusing populations. Special consideration should be given to a specific screening or diagnostic tool, or to a specific measure of treatment readiness, treatment compliance, service utilization, therapeutic process or drug treatment outcome.

24. *Behavioral Treatments for Pre-Adolescents and Adolescents.* Behavioral treatments for pre-adolescents and adolescents that incorporate HIV risk reduction counseling as an integral component of the treatment. This includes the development of new, or refinement of existing psychotherapies, behavioral therapies, and counseling (group and/or individual). This also includes the development and testing of manuals as well as other creative, interactive approaches for therapy delivery that may consider different settings for delivery, such as primary care, school-based health programs, juvenile justice settings, etc. Also the behavioral treatments should be culturally and gender sensitive.

25. *Behavioral Treatments for Couples and Families*. This includes the development of new psychotherapy approaches, the modification or testing of existing behavioral treatments, and the design and/or testing of innovative clinical training and supervision methods for dissemination of efficacious treatments to community settings. Treatments that target domestic violence or other forms of interpersonal abuse along with substance abuse are encouraged.

26. *Behavioral Treatments for Groups*. This includes the development of new psychotherapy approaches, the modification or testing of existing behavioral treatments, and the design and/or testing of innovative clinical training and supervision methods for dissemination of efficacious treatments to community settings. Examples of relevant projects are: traditional group therapies, such as 12-step and therapeutic community approaches, and newer group therapies such as cognitive-behavioral and acceptance-oriented approaches; groups for various populations, such as adolescents, adults, couple and family groups, gender-specific groups, and groups tailored for racial or ethnic minority populations. Of particular interest are projects that address the recent reports suggesting possible contraindications of group treatments for some populations (e.g., delinquent adolescents), or in some formats (e.g., less-structured, client-led groups).

27. *Behavioral Treatments Drawing from Stress Research or Stress-Management Interventions*. Projects are encouraged that apply concepts from stress research (such as appraisal, coping, and social support) to drug abuse in innovative ways, or that test the extent to which stress-management interventions can be applied to the treatment of drug abuse and interventions to reduce risk of HIV and other infectious diseases.

Examples of stress-management techniques that may have novel application to drug abuse and HIV risk include techniques that teach problem-solving and affect-management, restore one's sense of purpose and meaning, prevent burnout in the face of chronic stressors, increase self-efficacy for managing stress, inoculate against stressors, train relaxation and meditation, intervene during crises, enlist social support and system support, and others.

28. *Marijuana Treatment.* Marijuana is the most commonly used illicit substance in the U.S. However, relative to other drugs of abuse, little research has focused on the treatment of marijuana dependence. Trends in the literature suggest that the types of treatments effective with other substances of abuse are likely to be effective with marijuana dependence. Initial studies also suggest that many patients do not show a positive treatment response, indicating that marijuana dependence is not easily treated. This solicitation requests research aimed at developing and testing effective interventions for marijuana dependent individuals.

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29. *Transporting Behavioral Treatments to Community Practitioners*. There is a need for effective methods of transferring behavioral treatments found to be effective in clinical trials to clinical practice. Cognitive-behavioral therapy, operant behavioral therapy, group therapy, and family therapy are among the therapies that have been shown to be efficacious in a highly controlled setting and may be helpful treatment approaches in community treatment programs as well. However, community practitioners may have been trained using other approaches and may not have been exposed to these scientifically based approaches. This is a call for proposals that examine mechanisms to transfer effective research-based drug abuse treatment information and skills-based techniques to practitioners in the community. This may involve the development and testing of innovative training materials and procedures to use in the training of community practitioners to skillfully administer these treatments, including the development of highly innovative technology transfer and communication approaches. Research testing the transportability of empirically supported therapies to the community is an important component of the Behavioral and Integrative Treatment Development Program.

    There is also a need for the development of educational methods to train non-drug abuse health care workers in relating to drug abusers; eliciting medical histories regarding past or present drug abuse; recognition of the signs and symptoms of drug abuse; identification of those at high-risk for HIV and other drug abuse related medical problems such as tuberculosis or hepatitis. Development and validation of a drug abuse screening instrument which can be administered by primary health care providers, and training in administering such an instrument is also needed.

30. *Innovative Technologies for Drug Abuse Treatment, HIV Risk Reduction, and Training Clinicians*. Relevant research would be directed at the development and evaluation of innovative technologies to treat substance abuse, enhance adherence to medications, and/or reduce risk for HIV infection or transmission. Approaches should be capable of being readily incorporated at reasonable cost into various treatment settings. Areas of interest include Internet-based treatment or training programs, CD-ROM technology, audio delivery devices, photo therapeutic instruments, and hand-held computers. Also of interest are creative approaches for disseminating science-based behavioral treatments and for training therapists to use scientifically based treatments for drug abuse and addiction. Such approaches might include Internet-based education, interactive computer programs, telemedicine, etc. Finally, approaches which apply therapies with

evidence of efficacy through new media such as web-based platforms, over email, or through chat rooms and bullet boards are also desirable.

31. *Virtual Reality Applications for Drug Abuse*. Development and improvement of treatments using Virtual Reality and other new technologies is needed. New technology may help to make existing treatments more effective, or may make novel treatments possible. Behavioral treatment research to develop, modify, adapt, and test treatments for drug abuse and for comorbid psychiatric conditions (such as anxiety disorders) using new technologies is of interest.

    Recently virtual reality simulations have been used to train medical personnel in demanding medical procedures such as microsurgery techniques. Virtual training allows trainees to gain familiarity with both the environment in which services are delivered as well as the intervention techniques without the danger of mistakes impacting live patients. Virtual reality interfaces can assess skill acquisition and provide detailed feedback during procedures to help trainees correct mistakes or avoid making them altogether. In the drug abuse field, training and dissemination efforts have been hampered by a dearth of knowledge about ways to conduct dissemination. Although trainees often practice on actual clients, this approach has drawbacks including its reliance on the client or participant's schedule and willingness to participate in training sessions and potential danger to the client or if the intervention is delivered incorrectly. Libraries of virtual reality simulations of drug users in treatment or "virtual patients" are needed to provide experiential training for treatment providers without relying on existing patients. This will help facilitate the rapid and effective dissemination of proven treatment strategies.

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B. ***Clinical Neuroscience Research.*** The Clinical Neuroscience Branch (CNB) supports research on the biological etiology (determining the biological basis for vulnerability to drug abuse and progression to addiction, including studies on individual differences and genetics) and clinical neurobiology of addiction (exploring alterations of the structure and/or function of the human central nervous system following acute or chronic exposure of drugs of abuse), and the neurobiology of development (neurobiological effects of drugs of abuse and addiction during various stages of development and maturation, effects of drug exposure on neurobiological processes, development of methodologies and refinement of techniques used in pediatric neuroimaging). The Branch also supports investigations on the cognitive neuroscience of drug abuse and addiction, the neurobiology of treatment, neuroAIDS, and human pain and analgesia. Areas that may be of interest to small businesses include, but are not limited to:

1. *Development of Novel Approaches in Human Neuroscience.* Development of innovative, noninvasive research methods or novel approaches are needed to identify various neurobiological markers of brain alterations in humans induced by acute or chronic exposure to drugs of abuse. This may include the identification of neurobiological (including genetic) markers that might be associated with risk for, or resilience to drug abuse and addiction. Of particular interest are noninvasive methods (e.g., brain imaging) that could be used to determine the effects of drug abuse/ addiction treatments on neurobiological systems in an attempt to understand the neurobiological processes underlying therapeutic efficacy.

    In recent years, there has been an increase in studies employing functional magnetic resonance imaging (fMRI) to understand brain processes and functional neuronal systems. In particular, these neuroimaging techniques are being used to probe how

drugs of abuse alter brain functioning. Consequently, there is a need for the development of stimulus generation hardware to be used within an fMRI magnet that can display stimuli important in drug studies. As the studies of brain function become more sophisticated, task-related assessments of brain activation are increasingly important. Shielded goggles or other types of stimulus-generating hardware and software are necessary for presentation, for example, of neurocognitive tasks, drug-related images for the induction of craving, or other "virtual reality" types of dynamic stimuli important in studies of drug abuse and addiction. Responses to this type of stimulation then could be correlated with brain measures using neuroimaging techniques. These types of studies will provide new insights into drug-brain-behavior interactions.

Development of the human central nervous system and how drugs of abuse perturb this process is of great interest. Little is currently known about the effects of exposure to drugs of abuse, either prenatally or during childhood or adolescence, on the development of the human nervous system. Further, the application of newly emerging technologies (such as neuroimaging) to these populations presents unique challenges due to the fact that the central nervous system, and its capabilities, are changing rapidly. The development of novel techniques, or the refinement of existing methods, to provide direct noninvasive measures of brain structure and/or function that are adapted specifically for use in pediatric and adolescent populations is strongly encouraged. Also, neurocognitive and other neurobehavioral tasks for use in these populations, especially where they can be designed to probe underlying neurobiological processes, need to be developed (for developmental issues, contact Laurence Stanford, Ph.D.).

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2. *Virtual Reality for the Neurobiological Study of Drug-Brain-Behavior Interactions and Drug Abuse Treatment.* Virtual Reality (VR) is an emerging technology useful in a variety of research-related, therapeutic and instructional settings. By immersing a person's senses in a synthetic world or Virtual Environment (VE) that characterizes VR, a highly flexible and programmable set of stimuli can be used to enhance the standard approaches used in assessment of neurobiological and neurobehavioral processes.

   Collection of real-time data and bulk data recording can provide a correlation of a stimulus reference signal with simultaneously collected fMRI scanner and physiological data over time. Unlike most computer access systems that accept only one or two modes of precise and/or discrete input at a time, VR systems have the potential to monitor movement or action from any, or many, neurobiological functions at once. In addition, the multimodal feedback inherent in VR provides a way to vary nonvisual stimulus components (e.g., resistance, temperature, pitch) in a way that is impossible to achieve via standard computer systems. Finally, VR systems provide a bypass for keyboard entry or direct manipulation environments (e.g., pointing instruments like the mouse), by allowing the manipulation of multi-sensory representations of entire environments by natural actions and gestures.

   VE can provide a completely controlled, noninvasive, safe and alternative methodology for a variety of important studies of drug abuse and addiction. For example, VR allows

for the presentation of a variety of complex, multi-sensory stimuli for neurocognitive tasks or, alternatively, the dynamic stimuli important for producing drug-related images for the induction of craving. VR can also be tested as an alternative to traditional behavioral therapies in the treatment of drug abuse. Responses obtained as a result of the above can then be correlated with brain measures using state-of-the-art neuroimaging techniques. We, therefore, invite studies employing VR, especially to probe brain processes in drug abuse/addiction combined with neuroimaging methods or to be developed or applied as a potential treatment for substance abuse.

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3. *Development of Interactive Computer Applications for Neuropsychological/ Neurocognitive Assessment to Determine Functional Brain Deficits in Acute and Chronic Drug Abusers.* In addition, a neurobehavioral test battery to assess other neurobehavioral/neurocognitive deficits resulting from drug abuse/addiction is encouraged. Of particular interest is the development of such assessments for use in children and adolescents exposed to drugs of abuse to better define and understand the effects of early exposure on brain function and development (for developmental issues, contact Laurence Stanford, Ph.D.).

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4. *Development of Ligands for Brain Imaging.* Development of novel radioligands for PET and SPECT imaging in human brain for molecular targets (e.g., receptors, intracellular messengers, disease-related proteins) is of broad interest to the neuroscience and drug abuse research community. The primary application of these radiotracers will be in basic neuroimaging research. Ultimately, these radiotracers may also be used as potential biological markers and surrogate endpoints for translational and clinical research, drug discovery and development, and clinical trials. The scope of the projects may encompass pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. Alternatively, the focus may be on research and development of new technologies for radiotracer development.

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5. *Novel Approaches in the Clinical Neurobiology of Drug Addiction.* Many scientists involved in behavioral and neurobiological research are faced with growing difficulties in identifying approaches, devices (e.g., research tools) and/or strategies to broaden the within-discipline knowledge base for understanding, preventing and treating drug abuse. NIDA has a strong interest in facilitating the identification and use of cross-disciplinary research tools and materials that are being used and have proven efficacious in research unrelated to drug abuse (e.g., virtual reality, transcranial magnetic stimulation, deep brain stimulation). NIDA also has a strong interest in promoting the commercial

adaptation and widespread availability of discoveries (“tools”) made in the course of interdisciplinary research to better serve its mission.

The term research “tool" is being used in its broadest sense to embrace the full range of resources that scientists use in the laboratory and clinicians use as therapeutics; therefore, one investigator’s tool may be another's end product. The value of research tools is difficult to assess and varies greatly from one tool to the next and from one situation to the next. Providers and users are likely to differ in their assessments of the value of research tools. Many research and clinical tools are costly to develop and have significant competitive value to the firms that own them.

Advances in biomedical science continuously yield new research findings that play a critical role in the furtherance of knowledge and innovation in both the public and private sectors. For the purpose of this solicitation, the term research tool may include methods, laboratory equipment and machines, databases and computer hardware and software. From a clinical perspective, interactive games and emerging game technologies are being used successfully in a variety of health education situations; therefore, applications proposing introducing these “tools” as adjuncts in the prevention and treatment of drug abuse will be accepted. NIDA has solicited and continues to solicit proposals using virtual reality to increase our understanding of the neurobiology of addiction, (e.g., drug cues, craving), comorbidity (e.g., post-traumatic stress disorders) and pain (e.g., distraction). Additional novel approaches, devices and strategies are now being sought to further our understanding of the cognitive neuroscience of drug abuse and addiction, neuroplasticity and repair, the neurobiology of treatment (including training tools, assessment and neurolobiologic correlates of treatment outcome) and neuroAIDS.

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6. *Development of Serious Games for Neuro-Rehabilitation of Drug-Induced Cognitive Deficiencies.* Health-related gaming is an emerging industry useful in a variety of research-related, therapeutic and instructional settings. Serious games can provide a completely controlled, noninvasive, safe and alternative methodology for a variety of important studies of drug abuse and addiction.

   By involving a person in an interactive computerized situation, designed to be both entertaining yet directive (i.e., in the sense of covertly shaping desired behaviors via highly flexible and programmable sets of scenarios), altered behaviors can be introduced by pre-programming consequences to counteract and potentially reset undesirable neurobiological and neurobehavioral deficits associated with chronic drug abuse.

   It is hypothesized that changes in behavioral contingencies as a consequence of varying time and/or rate of the stimulus-response-reinforcer sequence (e.g., designing a game that involves differential rates for low responding (DRL) schedule) may alter brain activity (pattern changes noted using state-of-the-art neuroimaging techniques) and, thus, correlate with the improvement of neurocognitive deficits

   Neurocognitive deficits are generally drug-specific. For example, chronic methamphetamine abusers lose their decision-making ability, and suffer attentional bias in a visual discrimination task. Cocaine abusers lack cognitive flexibility, the ability to use feedback to monitor/change behavior, have slower reaction times on match-to-sample and increased errors (both omission and commission) along with attention/concentration deficits. Chronic use of opiates produces an increase in auditory, visual, and associative reaction times, impaired vigilance, attention, information processing, short-term visual

memory, delayed visual memory, short-term verbal memory, long-term verbal memory and problem solving. Although in controversy, marijuana may decrease one's ability to focus, sustain, and shift attention as well as decrease memory and motivation.

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7. *Development of Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and to Addictive Substances.* This announcement encourages the development, improvement and/or adaptation of measurement technologies for the purpose of creating field-deployable tools that can detect and quantify personal exposure to psychosocial stress and/or addictive substances with maximum precision and reliability. Ideally, the technology could be applied in large-scale population studies to comprehensively measure multiple addictive substances and psychosocial stress events, either singly or jointly. Comprehensive assessment includes measuring acute/chronic/cumulative exposures to psychosocial stress and/or addictive substances with a high degree of temporal and spatial resolution (i.e., as a person moves through environments), and with a high degree of accuracy and sensitivity to detect meaningful variations in extent of and response to exposure across developmental periods (ranging from prenatal to senescence) and among various population groups.

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C. ***Human Development Research.*** The Behavioral and Brain Development Branch (BBDB) supports a broad research, research training and career development programs directed toward: (1) an increased understanding of how developmental processes and developmental outcomes are affected by drug exposure and related factors; (2) an increased understanding of developmental processes that are relevant to: (a) drug use, abuse, addiction, treatment and relapse, and (b) risk behaviors related to drug abuse and other health conditions that often accompany drug use (*e.g.,* HIV infection, STDs); (3) the use of translational approaches to increase understanding of these developmental processes; and (4) an increase in effective interventions aimed at preventing or ameliorating negative developmental outcomes resulting from exposure to drugs and related factors.

1. *Develop Improved Technology for Assessment of Prenatal Drug Exposure and Passive Postnatal Drug Exposure.*

   a. Develop and refine methods for the detection and quantification of infant exposure to drugs of abuse during pregnancy, including cocaine, marijuana, opiates, and methamphetamines.

   b. Develop and refine methods for the detection and quantification of passive exposure to illicit drugs during infancy and childhood.

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2. *Develop Interactive Database Systems on Human Subjects Issues for Use by Drug Abuse Researchers Studying School-Age Children and Adolescents Drug Use.* Develop systems to assist investigators in obtaining technical and legal information relevant to involvement of children and adolescents in research on drug abuse. Examples of pertinent situations include tracking long-term health and development of children exposed to drugs during pregnancy, and investigating vulnerability and possible

pathways to drug abuse among school-age children and adolescents. These database systems should address issues such as assent and consent, should provide information on variation in laws and guidelines across jurisdictions, should include the capacity for interactive communication on numerous situations potentially facing investigators, and should serve as sources of referral for additional assistance.

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3. *Develop Improved Methods of Neuroimaging to Assess Structural and Functional Status of the Brains of Children and Adolescents Exposed to Drugs.* Document the feasibility and accuracy of appropriate and acceptable methods for assessing brain structure and function of children and adolescents, with special attention to any or all of the following groups: those exposed to drugs during pregnancy, those passively exposed during infancy and childhood, and those actively using illicit substances. Documentation should include attention to such matters as technological difficulties and risks, and standardization issues relevant to testing conditions and image analysis.

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4. *Develop and Refine Methodologies for Drug Use Measurement Among Adolescents.* Research to develop and refine methodologies for drug use detection and quantification, with special application to the adolescent with HIV infection or at high-risk for HIV infection. This research should address issues of acceptability, reliability, and validity of one or more methods (e.g., interviews, computerized questionnaires, and biological indicators such as saliva or sweat).

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Office of Science Policy and Communications (OSPC)

Science Education. In order to improve science education in the area of drug abuse research (e.g., disciplines such as neuroscience, psychology, epidemiology), efforts are needed to develop innovative methods for improving knowledge of and generating interest in science among school children, the general public, health care providers, and others. These might include but are not limited to:

- Development of methodologies to present drug abuse and science information to particular groups, such as kindergarten and elementary school students, African Americans, Hispanics, persons with disabilities and health care providers.

- Development of methodology to transfer new knowledge and directions of scientific growth to teachers, curriculum developers and health care providers.

- Development of computer based learning systems that allow students to experience the scientific process.

- Development of specific materials, activities, or programs that promote science education related to drug abuse, such as exhibits, curriculum materials, coloring books, videos, teacher education workshops, partnership programs with scientists and educators, or workshops for health care providers.

- Development of specific materials, activities or programs that promote the teaching of scientific and research ethics to middle and high school students.

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International Program

NIDA's International Program develops and disseminates important new information on the causes, consequences, prevention and treatment of drug abuse and addiction that will help address the growing problems related to illegal drug use and addiction around the world.

NIDA's International Program is currently interested in supporting US-based small businesses to develop products and services in the following areas:

1. Development of accurate and culturally-appropriate translations of valid and reliable questionnaires, surveys, interviews, and other instruments for use in domestic and international settings. Other instruments may include assessment, quality of life, and outcomes measures.
2. To facilitate research collaborations between U.S. and international researchers, and to respond to the demand for science based drug abuse information, there is a need for the development of a series of information and training modules specially targeted to foreign trainees and investigators. Proposed topics for the modules include, but are not limited to: Drug Abuse Treatment Approaches, Understanding the Neuroscience of Addiction, Tools and Guidelines for Assessing and Evaluating Drug Abuse Treatment Programs and Treatment Approaches with HIV-Positive Drug Abusers.
3. Development of standardized behavioral, physiological, and/or toxicological measures of drug use and drug impairment for use in international comparative studies of drugged driving.
4. Development of a mechanism to enhance international drug abuse researchers' ability to conduct secondary data analyses. While the strategies to address the international phenomenon of drug addiction need to be empirically driven, there are limited funds to support original international drug abuse research which subsequently increases the importance of secondary analyses of existing data sources particularly in low- and middle-income countries. The mechanism to expand the use of existing data sources that can inform policy is likely be multifaceted and may include: identification of existing data sources, provision of training in secondary data analyses, and interpretation of data analyses for making policy-based decisions. The focus of the research can address any component of drug use, abuse and addiction that is within NIDA's research portfolio.

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Other Research Topic(s) Within the Mission of the Institute

NIDA encourages applications in other areas of research that may not be listed.

For additional information on research topics, contact:

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