DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The purpose of this application is to develop a Consortium for the "Collaborative Initiative on Fetal Alcohol Spectrum Disorders" (CIFASD). The CIFASD will coordinate basic, behavioral, and clinical investigators in a multidisciplinary research project to better inform approaches aimed at developing effective intervention and treatment approaches for FASD. It will involve the input and contributions from basic researchers, behavioral scientists, and clinical investigators with the willingness to utilize novel and cutting edge techniques, not to simply replicate previous or ongoing work, but rather to move the field forward in a rigorous fashion. The first step is to definitively outline a diagnostic schema so that the full range of effects from prenatal exposure to large or moderate amounts of alcohol can be determined. While an abundance of evidence exists on the outcomes following prenatal alcohol exposure, one of the hindrances to developing a full set of criteria for diagnosing FASD has been the lack of adequate numbers of subjects at any single research site. This consortium will integrate researchers from a number of sites, including several international locations, to share common protocols, so that a large number of individuals can be assessed using similar procedures. These sites will interface with cores providing expertise in dysmorphology, behavioral assessment, and brain imaging. We will intergrate the data collected at the various sites in the various domains (dysmorphology, behavior, brain) to develop a comprehensive assessment battery. At the same time, we will develop state of the art methodology to better define the diagnosis and the full range of effects resulting from prenatal alcohol exposure. This consortium will also include basic science components, whose long-range goals are aimed at developing effective interventions. The basic science components will inform the clinical components and vice versa. All projects and cores will interface with the Administrative Core and the Informatics Core to provide for the flow of information between the various PIs involved in this consortium. The purpose of this consortium is to provide the answers to much needed questions as it relates to the full spectrum of consequences redulting from prenatal alcohol.

PERFORMANCE SITE(S) *(organization, city, state)*
San Diego State University, San Diego, CA
Harvard University, Boston, MA

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
Riley, Edward	San Diego State University	PI-Adminstrative Core
Charness, Michael	Harvard University	Scientific Director
Thomas, Jennifer	San Diego State University	Research Specialist
Foroud, Tatiana	Indiana University	Steering Committee Member
Jacobson, Sandra	Wayne State University	Steering Committee Member
Jones, Kenneth Lyons	University of California, San Diego	Steering Committee Member
Mattson, Sarah	San Diego State University	Steering Committee Member
May, Philip	Univeristy of New Mexico	Steering Committee Member

Disclosure Permission Statement. Applicable to SBIR/STTR Only. See instructions. ☐ **Yes** ☐ **No**

I. Themes and Goals of the Consortium

A. Specific Aims: The purpose of this application is to develop a Consortium for the "Collaborative Initiative on Fetal Alcohol Spectrum Disorders" (CIFASD). In maintaining the language of the RFA, the term "fetal alcohol spectrum disorder" (FASD) is used throughout to signify the range of possible outcomes resulting from exposure to alcohol *in utero*. We are not endorsing FASD as a specific diagnostic term, but rather, as an umbrella term that recognizes the entire range of possible outcomes resulting from prenatal exposure to alcohol.

The theme of this collaborative initiative is a cross-cultural assessment of FASD. The CIFASD will coordinate basic, behavioral, and clinical investigators in a multidisciplinary research project to better inform approaches aimed at developing effective intervention and treatment for FASD. Input and contributions will come from basic researchers, behavioral scientists, and clinical investigators who are willing to utilize novel and cutting edge techniques, not simply to replicate previous or ongoing work, but rather to move the field forward in a rigorous fashion. We believe that a first step in developing effective interventions and treatments is to definitively outline a diagnostic schema so that the full range of effects from prenatal exposure to large or moderate amounts of alcohol can be determined. While an abundance of evidence exists on the outcomes following prenatal alcohol exposure, one of the hindrances to developing a full set of criteria for diagnosing FASD has been the lack of adequate numbers of subjects at any single research site. This has limited the generalizations that have been possible from any single research location, and the control of a number of potential intervening variables. Therefore, this consortium will integrate researchers from a number of sites, including several international locations, to share common protocols, so that a large number of individuals can be assessed using similar procedures. With such collaborations, it will be possible to answer questions that could not be answered easily by data from any individual study site. Furthermore, replication between sites differing in population and environmental characteristics would provide converging evidence for specific patterns of effects resulting from prenatal alcohol exposure. The consortium was also developed with the idea that only a subset of important issues could be addressed in this initial application, but that the members of this consortium, with the advice and guidance of the Scientific Advisory Board, would develop other research projects as a group and implement these during the life of the consortium. In this way the consortium is seen as a dynamic enterprise capable of posing and answering questions in a realistic time frame.

The Specific Aims are as follows:

1. Utilizing several sites with samples of varying ages and demographics, we will establish procedures for better defining and characterizing the range of outcomes from prenatal alcohol exposure. This will be accomplished by the establishment of a diagnostic group that would include the scientific cores for the study of dysmorphia, neuropsychological and behavioral functioning, and brain imaging. Within this aim, new, innovative techniques will be assessed and then implemented as indicated by the data collected. This will help in defining characteristics indicative of prenatal alcohol exposure that can be assessed easily and reliably.

2. With the realization that no single research site will have enough subjects to adequately address many of the questions posed in this application, this consortium will build upon existing research programs on FASD, including several international programs. Some countries have much higher rates and levels of alcohol consumption during pregnancy and of FASD than in the United States. Moreover, additional sites are being identified, each with unique attributes, so that they can be incorporated into the consortium through pilot or developmental projects. Our goal is to obtain concordance on a set of diagnostic criteria between sites, basing these criteria on the diagnostic techniques established in Aim #1.

3. A Basic Science Program seek to uncovering the basic mechanisms involved in alcohol teratogenesis and to design effective interventions to mitigate or prevent the effects of prenatal alcohol exposure. The Basic Science Program will utilize a spectrum of models, from molecular analysis of alcohol antagonist actions to prenatal ethanol effects in mice, rats, and sheep. Basic Science Projects will be integrated through a common focus on neural systems that are vulnerable to ethanol in humans,

diagnostic procedures that are currently employed in infants, and effects of agents that prevent ethanol teratogenesis. The Basic Science Program and the Clinical Programs will work collaboratively to translate fundamental scientific observations into clinically useful diagnostic tools and treatments.

4. The Consortium will attract new and innovative investigators to the study of FASD by recruiting individuals for the development of U01 grants and pilot projects. The Consortium will target experts in fields related to this proposal who are not currently involved in alcohol research.

5. To utilize the information obtained from the various projects to secure additional funding to implement innovative interventions and treatment strategies on a wide scale.

6. To make available the data collected through this consortium to scientists, practitioners, government agencies, and caregivers of individuals with FASD worldwide, by providing our results and data sets through the internet. It is our belief that information gained from this consortium must find its way into the hands of individuals who deal with individuals with FASD as easily and as quickly as possible, so that the findings can be implemented without delay.

B. Background and Significance

Goals of the Consortium. As stated, our theme is one of a cross-cultural assessment of FASD and the overall goals of this consortium are: 1) To better define the effects from prenatal alcohol exposure, including new methodologies to define the fetal alcohol syndrome (FAS) and other alcohol related neurodevelopmental disorders (ARND); 2) To develop more accurate ways of ascertaining these effects and then implement their assessment on a broad scale; 3) To involve researchers from around the world in these various projects, and to engage researchers from outside the alcohol field in the hopes of bringing new techniques and new ways of thinking to the FASD problem; 4) To develop effective interventions and methods to mitigate the effects of prenatal alcohol exposure; and 5) To make any findings available to those interested in the problem of FASD, be they lay persons, practitioners, or researchers.

These goals are set around specific questions that will be addressed by one or more sites engaged in consortium research. The rationale and the specific questions can be posed as follows.

1. Although there is wide recognition that the most devastating consequence of prenatal alcohol exposure impact brain and behavior, unfortunately, we do not currently have a behavioral profile that can be used effectively to screen for prenatal alcohol effects. A primary goal of this consortium is to identify behavioral profiles that are indicative of prenatal alcohol exposure. We believe that multiple profiles will be needed to reflect differences in the timing or dose of exposure, the age of testing, and other factors. Therefore, the first question is: Can behavioral profiles be determined that are characteristic of prenatal alcohol exposure?

2. Currently, the diagnosis of FAS is dependent upon three criteria: growth retardation, CNS anomalies, and importantly specific facial dysmorphia. FAS is not an easy diagnosis to make and different physicians often utilize different criteria. The second question is: Can we determine a specific set of criteria with precise measurements in areas of facial dysmorphology, brain imaging, and neurobehavioral profiles that can be utilized in the diagnosis of FAS and broadly applied?

3. While the face of FAS may be somewhat distinct, it is our belief that subtle changes in the face might occur in individuals with a history of prenatal alcohol exposure, but without the facial features typical of FAS. Furthermore, we believe that early diagnosis is critical, and that the diagnosis of prenatal alcohol exposure in infants is an important goal. Our third question is: Can subtle physical signs, brain alterations, and facial characteristics be better utilized to help define prenatal alcohol exposure and can at least some of these physical signs be evaluated early in life to help diagnose infants at specific risks?

4. While both physical and behavioral diagnosis are extremely important, a crucial goal of this RFA and this consortium is to provide a mechanism for testing novel interventions. Our fourth question is: What interventions are effective in mitigating the effects of prenatal alcohol exposure?

5. Animal models of FASD have proven very useful in the study of prenatal alcohol exposure. It is our belief that understanding the mechanisms by which prenatal alcohol exposure exerts its effects will lead to potential interventions. This is viewed as a long-term, but nonetheless, important goal. This leads to the fifth question of: Can our basic research projects inform the clinical studies in providing a rationale for intervention efforts?

Rationale and theme for the CIFASD

It has been 30 years since Jones et al. (Jones et al. 1973a; Jones et al. 1973b) identified the Fetal Alcohol Syndrome (FAS), and since those seminal reports, thousands of articles have appeared on various aspects of prenatal alcohol exposure. Initially, attention was directed toward identifying the scope of the problem, how many people were affected, the behavioral and physical effects of prenatal alcohol exposure, and potential mediating mechanisms. We soon learned that FAS was not simply a problem in the United States, but rather it was a problem of international scope. In fact, shortly after the publications by Jones and colleagues, it was discovered that Lemoine had reported similar findings in a group of French children about 5 years earlier (Lemoine et al. 1968). Wherever heavy drinking during pregnancy occurs, FAS is going to be detected. By 1990, articles on FAS had been published in over 20 different languages from countries representing all of the inhabited continents.

The theme of a cross-cultural longitudinal assessment of FASD grew specifically out of two international meetings on FAS. The first held in Missillac, France in 1997 involved representation from six countries (Riley 1998). More recently, an international FAS meeting was held in Valencia, Spain, in which ongoing international collaborations were reviewed and the prospects for new collaborative research explored (Riley et al. 2003). The attendees represented nine different countries and many different specialties. The Valencia meeting grew out of the premise that the effects of prenatal alcohol exposure were a universal problem and that we could better understand these effects, and their prevention and treatment, if we studied them from that perspective. Common themes link findings from the United States, Eastern and Western Europe, South Africa, and South America. Given the diverse drinking practices, prenatal care, rearing practices, and methods of evaluation that occur across countries and cultures, the fact that there is a major degree of similarity in the findings lends a great deal of credence to the results. It also provides for an incredible opportunity to use this diversity for collaborative studies to better understand the problem in total. That is one of the aims of this consortium.

The goal of this consortium is to bring together researchers from around the world who are conducting research on FASD or interested in the global problem of FASD and who have the capabilities and resources to utilize international samples to further knowledge in this area. Advances in science often require the appropriate technological, social and cultural climates to foster those advances. As aptly put by Dr. Faye Calhoun during the Introductions of the Valencia meeting (Riley et al. 2003), the time for FAS collaboration is ripe and advances that could not have been conceived 5 or 10 years ago are now possible because of these collaborations. Several themes resulted from that meeting and some of them are addressed in this consortium. The convergence of data from different populations provides a strong relationship between alcohol exposure and outcomes and the availability of large numbers of subjects greatly enhances the power of any study. Studies that could not be conducted in any one site due to lack of subject numbers or given expertise, become possible in collaborative efforts such as those proposed here. As an example, since the Valencia meeting, another meeting was held in Indianapolis, in 2002, to begin sharing data on the neurobehavioral effects of prenatal alcohol exposure, utilizing data collected in South Africa, Moscow, San Diego, Detroit, Atlanta, and Albuquerque. One abstract has already been presented utilizing a combined data set (Flury et al. 2003) compiled from that meeting. Data are being pooled with the hopes that we can begin to answer questions related to specific domains in which behavioral function might be compromised. Rather than a single site with perhaps fewer than 50 subjects under study, several hundred subjects are now being employed in the search for answers to longstanding questions. Opportunities abound and new international collaborations are being discussed or are in the early stages of implementation. FASD is a worldwide problem and when it is addressed as such, there is a tremendous potential for progress. That is the hope and vision of this consortium. Among the themes addressed in this consortium are: the interrelationship between basic science and clinical studies and intervention, the importance of developing a behavioral profile for individuals with

histories of prenatal alcohol exposure over a range of ages and cultures, the importance of identifying risk factors, the need for specific criteria for the FAS diagnosis and improved capabilities for making the diagnosis of FASD, and the assessment of potential interventions.

Currently, the diagnosis of FAS is fairly well recognized. As stated, FAS consists of a triad of facial dysmorphology, growth deficits, and evidence of a CNS abnormality. However, many physicians feel uncomfortable making the diagnosis, resulting in a gross underrecognition of FAS. For example, in a study of Massachusetts' physicians, a substantial proportion had knowledge about the effects of alcohol on pregnancy, but felt unprepared to deal with this topic. Physicians frequently did not make a diagnosis even when they suspected FAS, and one reason for this might be hesitancy to diagnosis in the absence of very obvious signs. More physicians suspected FAS/FAE than made the diagnosis and almost 75% felt additional education would be helpful (Morse et al. 1992). Furthermore, Abel and Kruger (Abel et al. 1998) found that physicians were generally misinformed about what constituted a risk-level of drinking and hence this also interfered with the diagnosis. One of the aims of this consortium is to enhance the ability to diagnose FASD by utilizing a group of dysmorphologists who have seen more cases of FAS than any other group in the world, as well as the latest imaging and facial recognition technologies, to determine exactly what constitutes the face of FAS, and what criteria need to be considered in the diagnosis. Additionally, brain imaging and behavioral studies will also be utilized to assist in the diagnosis.

In addition to issues with the diagnosis of FAS, a much larger problem exists in the diagnosis of children affected by prenatal alcohol exposure, who lack defining facial dysmorphia. These children have received labels such as FAE (fetal alcohol effects) or ARND (alcohol related neurobehavioral dysfunction). The clinical challenge is to determine if the behavioral effects noted are truly the result of the alcohol or rather, due to other environmental, genetic, or demographic factors. What is necessary in this case is to define a behavioral phenotype or phenotypes that are indicative of prenatal alcohol exposure. For example, children exposed to alcohol prenatally have very high rates of attentional deficits. However, how does one know if the attentional deficit noted is the result of prenatal alcohol exposure or of some other cause? By assessing a range of cognitive and behavioral domains, it is hoped that a phenotype(s) can be identified that would point to prenatal alcohol in the etiology of the behavioral dysfunction and assist in the diagnosis of FASD. The importance of accurate diagnosis is emphasized by data indicating that early intervention is effective in ameliorating many of the "secondary disabilities" associated with prenatal alcohol exposure (Streissguth et al. 1996). Furthermore, there are data that standard pharmacological treatments of attentional deficits (e.g. ADHD), such as methylphenidate, may not be as useful in cases where the underlying etiology is fetal alcohol exposure. This consortium will try to address this issue by assessing a wide range of behavioral domains across different populations to determine which domains and specific behaviors appear to be most affected by prenatal alcohol exposure.

Consortium Strengths

This Consortium has several strengths. First, it brings together individuals with significant experience with FASD. This group of clinical and behavioral investigators perhaps has more experience with individuals with FASD than any other group that could be put together. By collaborating and meeting on a regular basis much more can be accomplished than in any one laboratory. Second, this consortium studies populations with known high rates of alcohol abuse and a high incidence of FASD. For example, the rates of FAS among the groups being studied in South Africa are over 75 per 1000. Rates of FAS in Moscow, Russia are also high. This allows for a large number of affected individuals to be readily assessed using common assessment batteries. Third, the Consortium provides for assessment in a number of domains, from classic dysmorphology to subtle brain changes. It incorporates a strong basic science program aimed at determining potential pharmacological interventions. Next, all participants view the consortium as a dynamic entity, where research priorities can be addressed in a scientific and timely fashion. For many of the participants, FASD has been a lifelong field of study and the single most important belief among the participants is that we can make a difference in altering the outcomes from the tragic consequences of prenatal alcohol exposure. Finally, the consortium addresses many of the concerns expressed in the RFA. It contains Cores and/or Projects related to administration, informatics,

dysmorphology, brain imaging, intervention, behavioral phenotyping, and animal model work, all of which were pointed out in the RFA to be areas that the Consortium needed to or might address.

II. The structure of the Consortium – Overview.

The present proposal will integrate research sites with large samples of individuals with FASD located worldwide as well as strong basic science laboratories conducting FASD research. Studies will be conducted across several domains (physical models, behavioral models, brain imaging models). Core facilities will provide resources to these sites and allow collaborations between the sites although the individual research sites will propose their own projects in addition to the collaborative projects. The individual research sites bridge to each other through the cores, while answering important questions relevant to either the physical, behavioral or brain changes seen in FASD. Obviously, the physical features noted in the dysmorphology core and the facial imaging cores will help to inform the behavioral and imaging questions, but similarly as the focus of this project moves from FAS to FASD, the behavioral and brain imaging cores should help to focus the dysmorphology and 3D facial imaging cores, to more subtle and perhaps more specific outcomes. The basic science group should inform the clinical studies, and new ideas related to clinical interventions can be tested initially by the basic science group.

The administrative and informatics cores are seen as central to the consortium and form the means by which information will be monitored and flow between projects. Progress and goals can be monitored and modified based upon findings from the various projects. This consortium is viewed as dynamic, building upon information gained from the projects and from the input of the Science Advisory Board to pose new questions and integrate new techniques to assist in the intervention and prevention of FASD.

While some of the projects proposed in this application could be completed independent of the Consortium, it is unlikely that the results would be generalized or the questions would be answered with the same speed and precision. No individual site has the population of FASD individuals made available by this consortium. Similarly, the power offered by converging data across sites allows for control of demographic variables not possible with a single study site. It is the belief of the members of this consortium, that it is this convergence of data across sites that provides a major benefit of the consortium. Data that replicate across sites will indicate with firmer conviction that the changes noted following prenatal alcohol exposure are related to the teratogenic actions of alcohol, rather than to other mediating factors. An international data set will also allow for more specificity in defining the characteristics resulting from prenatal alcohol exposure. If not all sites replicate each other, it will establish that there are intervening variables that may play a protective or synergistic role, and allow the consortium to move towards defining those variables. These are advantages that are simply not possible in a single site project.

Structure and composition of the Consortium – details. The structure of the proposed consortium is as follows:

Consortium Coordinator:

PI and Consortium Coordinator,
Chair of the Steering Committee,
Edward P. Riley, San Diego State University

Co-Chair of the Steering Committee,
Scientific Director, Steering Committee,
Michael Charness, Harvard Medical School, Boston VA Hospital

Steering Committee (current)

Tatiana Foroud, Indiana University
Sandra Jacobson, Wayne State University
Kenneth Lyons Jones, University of California, San Diego
Sarah Mattson, San Diego State University
Philip May, University of New Mexico

Cores:

CORE 1 U24: Administrative Core, Edward P. Riley (SDSU)
CORE 2 U24: Informatics Core, Craig Stewart (Indiana University)
CORE 3 U24: Pilot Project Core, Edward P. Riley (SDSU)

PILOT PROJECT 1 Pilot Project – FASD in the Ukraine. Kenneth Lyons Jones, M.D., UCSD.
PILOT PROJECT 2 Pilot Project – A FASD epidemiology in Italy. Philip May, Ph.D., University of New Mexico.
PILOT PROJECT 3 Pilot Project – Detecting FASD from neonatal ultrasound. Ann Streissguth. Ph.D., University of Washington.
PILOT PROJECT 4 Pilot Project – Comparison of three diagnostic modalities in FASD and related disorders. Luther Robinson, SUNY-Buffalo

Clinical Group of Cores

CLINICAL CORE 1 U24: Dysmorphology Core, Kenneth Lyons Jones (UCSD)
CLINICAL CORE 2 U24: Neurobehavioral Core, Edward P. Riley (SDSU)
CLINICAL CORE 3 U24: 3D Facial imaging Core, Tatiana Foroud (Indiana University)
CLINICAL CORE 4 U24: Brain imaging Core, Elizabeth Sowell (UCLA)

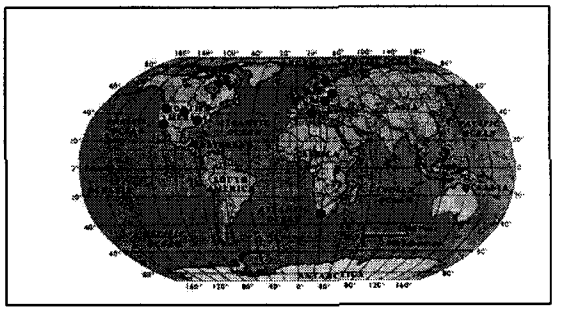
Clinical Projects

CLINICAL PROJECT 1 U01: Risk Factors for FASD in the Moscow Region. Christina Chambers, Ph.D., UCSD.
CLINICAL PROJECT 2 U01: FASD in San Diego and Moscow. Sarah Mattson, Ph.D., SDSU.
CLINICAL PROJECT 3 U01: Multi-method intervention study of FASD in South Africa. P.W. Kodituwakku, Ph.D., University of New Mexico.
CLINICAL PROJECT 4 U01: Identification of FASD in South African Children. Sandra Jacobson, Ph.D., Wayne State University.
CLINICAL PROJECT 5 U01: International neuropsychological study of FASD. Philip A. May, Ph.D., University of New Mexico.
CLINICAL PROJECT 6 U01 Neurobehavioral outcome in adolescents with FAS and FASD – Ilona Autti-Rämö, M.D., Helsinki University Hospital, Finland
CLINICAL PROJECT 7 U01 FASD: Fetal alcohol exposure: Neurophysiology and development. Claire Coles, Ph.D., Emory University.

Basic Science Group

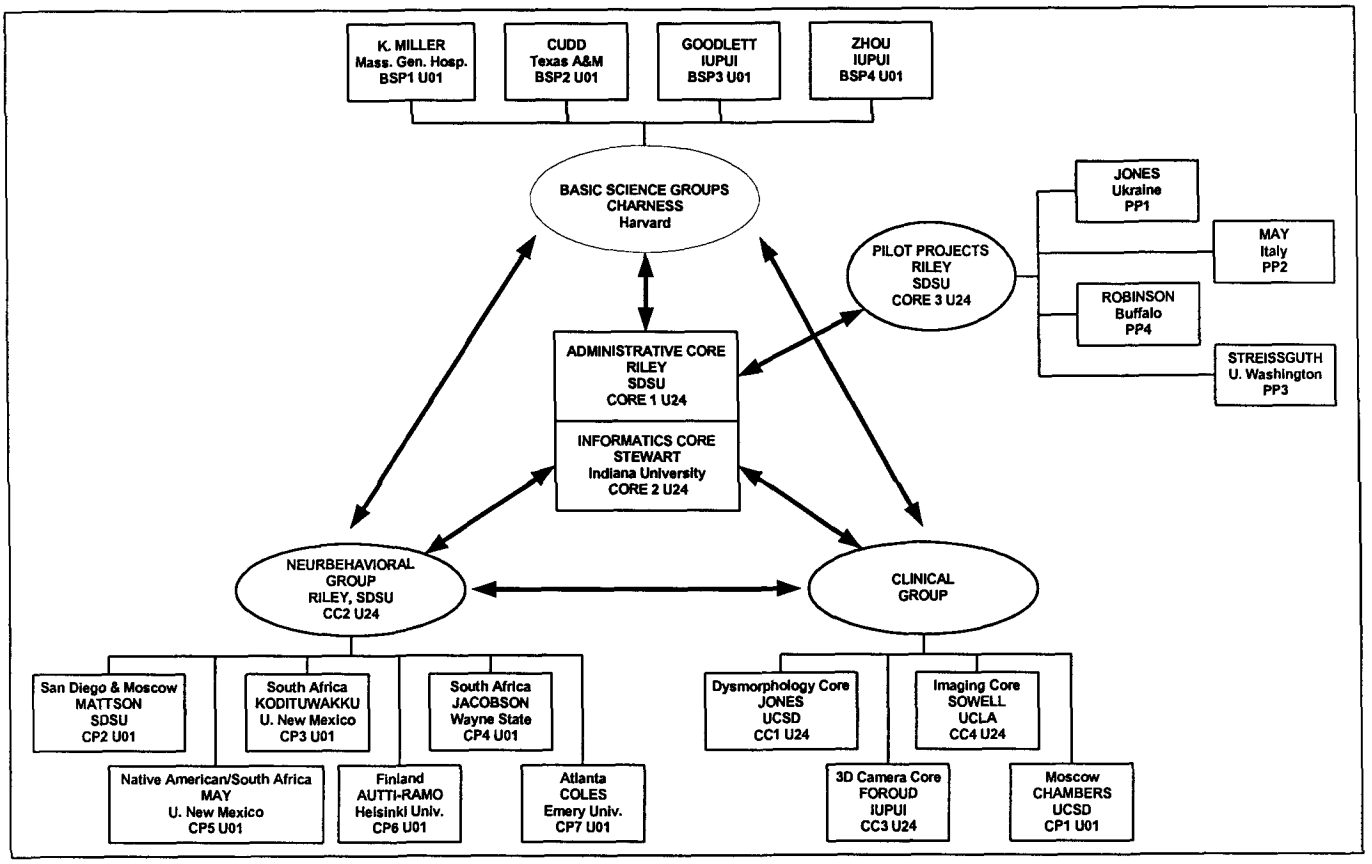
BASIC SCIENCE PROJECT 1 U01 Photolabeling of alcohol binding sites L1. Keith Miller, Ph.D. Massachusetts General Hospital
BASIC SCIENCE PROJECT 2 U01 Testing FASD therapeutic agents: Sheep model. Timothy Cudd, D.V.M., Ph.D., Texas A&M.
BASIC SCIENCE PROJECT 3 U0 1 Testing FASD therapeutic agents: Neonatal rodent models. Charles Goodlett, Ph.D., Indiana University
BASIC SCIENCE PROJECT 4 U01 Testing FASD therapeutic agents in C57/BL mouse model. Feng Zhou, Ph.D., Indiana University

III. Structure of the Cores and Projects.



The Clinical Components are highly integrated and are comprised of sites from around the world (See Figure). U01 projects will occur in San Diego, Atlanta, New Mexico, Moscow, South Africa, and Finland and pilot projects in Seattle, the Ukraine, and Italy. Within each site, similar protocols supported by the Cores will be carried out where feasible (e.g. projects that deal with infants, of course, will not be utilizing the same protocol as projects dealing with older children). Where feasible we will collect similar data at each site.

The overall structure of the Consortium is depicted below.



Basic to this consortium is the Dysmorphology Core. The national and international experience of Kenneth Lyons Jones, Luther Robinson, and Gene Hoyme brings an incredible amount of expertise to this project. One of its goals is to ensure that each site in this consortium is using the same diagnostic rigor and criteria to diagnose FASD. It will be the responsibility of the Dysmorphology Core to assure accurate and consistent diagnosis of FASD in children at all consortium sites through implementation of a standard protocol based on documentation of the clinical phenotype. Thus, the Dysmorphology Core is expected to interact with each clinical component project. An important part of this interaction will be to train local pediatricians at each site, something that we feel strongly about. It gives something back to the communities and helps to ensure that even after these research projects end that there will be local pediatricians able to make the diagnosis. Another goal of this core is to determine with large sample size, the characteristics that best define the FAS phenotype (e.g. does prenatal weight or palprebral fissure size best determine the FAS phenotype?) The core should be able to gain new insight into a variety of issues relating to the clinical phenotype, including the full range of structural defects in the disorder, physical features that are predictive of alterations in neurobehavioral development, and the extent to which degrees of the various individual components used in the diagnosis will enhance specificity of diagnosis without loss of sensitivity. Another important aspect of this core is the assessment of neonates (Seattle, Moscow and Ukraine), because the diagnosis of FAS is currently difficult at this age. This consortium will allow an opportunity to develop strategies to diagnose this disorder early in life. Finally, because of the different ethnic groups under study, this Core should be able to discern the differences in various groups in response to prenatal alcohol. A common maternal alcohol ascertainment interview will be used in the different projects.

The Neurobehavioral Core will interact with each site by providing a common set of test protocols. Again, these protocols will be specific for the ages under study at each site. For example, the CANTAB, a computerized test battery will be used at all sites involving children and adolescents (Moscow, San Diego, Atlanta, Finland, New Mexico, and South Africa), but not at sites involving infants (e.g. Ukraine,

Moscow) where another battery will be utilized. The goal of this Core will be to help define specific behavioral profiles indicative of prenatal alcohol exposure. We have made progress in this endeavor and this consortium should make the behavioral diagnosis even more specific. For example, the vast majority of individuals with prenatal alcohol exposure have enough clinical signs to receive a diagnosis of one of the attentional disorders. A potential critical question for this core is to try and discern behavioral characteristics that can differentiate individuals with attentional disorders related to prenatal alcohol exposure from those with these disorders related to other causes. The Neurobehavioral Core will assess the behavioral data collected at each site and decide if new specific tests that may be only used at one site should be extended to other sites.

The Facial Imaging Core is a novel approach to the diagnosis of FASD. It will integrate initially with projects in Moscow, South Africa, San Diego, Buffalo, and New Mexico. The goal of this project is to better define the facial characteristics that might be associated with prenatal alcohol exposure, utilizing the latest in facial recognition software, morphometry, and 3D cameras. It will interrelate to the other projects as the results from the initial sites become known and the utility of this system is evaluated. This Core and the Dysmorphology Core will have to interact in that the facial imaging core will be attempting to computerize what the Dysmorphology Core is doing by more traditional means. The morphometry and facial recognition will only be as good as the dysmorphology data, until algorithms are developed that will hopefully capture those subtle signs that the dysmorphologist are utilizing to diagnose FAS, even if they are unaware those subtle criteria. Obviously, this Core will interact with the other Cores as well, as our belief is that subtle facial characteristics noted following prenatal alcohol might be indicative of changes in brain and behavior and help to diagnose FASD.

Extensive investigations into brain structural abnormalities in FASD have been conducted by the investigators of the Imaging Core who are leaders in the study of brain morphology in FASD. The Brain Imaging Core will be an integral part of the entire proposal, as it allows assessment of linkages between brain anatomy, and all other data types collected by Consortium members. These relationships can be depicted by creating brain maps that explicitly define regions where brain anatomy is correlated with neurobehavioral or facial morphological variables. State-of-the-art brain image analysis methodology such as we propose to use in the CIFASD is quickly advancing, highly technical, and requires considerable computing resources and extensive training. The Brain Imaging Core will bring all these aspects of their resources and experience to all Consortium members, significantly enhancing Consortium members' ability to exploit the expensive imaging data they will collect in their research projects. In turn, the Imaging Core will benefit from the other cores and projects by an enhanced understanding of correlates of brain dysmorphology resulting from prenatal alcohol exposure. It is expected that the number of sites conducting brain imaging assessments will increase considerably throughout the life of the consortium.

The Informatics Core will provide a critical part of the infrastructure enabling collaboration within the Consortium. The Informatics Core will work collaboratively with each of the other Projects, Cores, and Pilot Projects to arrive at a common data dictionary for all shared data, and will provide training and consulting assistance for addition, retrieval, and updating of information from the Consortium Data Repository. It will provide for data storage, quality assurance, data access, and data analysis to enable the Consortium to amass and properly analyze the large quantity of data that will be required to help understand FASD. In particular, the Informatics Core will support data management; maintain data stores in a reliable, secure fashion that will enable easy retrieval from properly authorized researchers; make data available via an Internet-accessible, secure, database; provide statistical and statistical computing support, and will support the Administrative Core in management of the Consortium by producing periodic and ad hoc status reports. It will also collaborate on statistical design and statistical computing with each of the other projects. The Informatics Core will periodically and informally survey the other participants in the Consortium to determine what adjustments should be made in the services provided and to ensure that the services provided by the Informatics Core are meeting the needs of the Consortium as a whole.

When this Consortium was being planned, we believed that a Biomarkers Core would be a tremendous addition to the project. We felt that a core where genetic analysis or where meconium assays could be

done would enhance the operation of the Consortium. We still believe this, but because of budgetary constraints, this core was eliminated. Lucinda Carr, from the Indiana Alcohol Research Center has agreed however, to assist some projects with DNA analysis or banking of blood for subsequent analysis (See supporting letter). If in the future we believe that the meconium assays would benefit or increase the reliability of our work, we will apply for additional funds for this purpose.

Research sites for this Consortium were specifically chosen for many reasons. First, the investigators at these sites all have a long history in FASD research, and many of them have been involved in this work since shortly after FAS was identified in 1973. Thus, project leaders bring an incredible amount of experience to this Consortium. Furthermore, many of them have worked together on previous projects and publications together. Second, as mentioned, one of the difficulties with research in FASD is the acquisition of subjects. Sites were chosen because they have access to reasonable numbers of subjects or have specific resources available to study those populations. The studies to be conducted in South Africa, allow access to a large number of subjects, good histories on prenatal alcohol exposure, availability of extended families for interviews, and a situation where the children are raised in the home and are attending schools in the community. In Moscow, the subjects all live in the same environments (orphanages). Thus, we are able to match exposed subjects with controls on IQ and environment, and large numbers of subjects are available for study. The Native American population provides another set of subjects available in relatively high numbers. Similarly, the populations available for study in Helsinki, Atlanta and San Diego have been studied for a number of years in ongoing research projects.

The proposed study of mothers and infants in Moscow under the direction of Dr. Chambers is interested in defining the range of expression, risk factors for, and incidence of FASD in children born to women who drink varying amounts of alcohol during pregnancy. This is a collaboration with the Moscow Region Ministry of Health and intends to screen 26,000 pregnant women over 2 years. From these, 640 moderate to heavy drinkers and 640 controls will be selected for longitudinal follow-up including standardized physical exams and neurobehavioral testing of infants through 12 months of age. This study will provide an estimate of the prevalence and range of alcohol-related effects in the neonates. Furthermore, it evaluates the contribution of maternal nutritional factors in the etiology of FASD and contains an intervention strategy utilizing micronutrients. This study will contribute to a better understanding of the incidence and range of FASD based on early diagnosis in a cross-cultural environment, and will for the first time, specifically test a nutritional intervention that may have widespread applicability should undernutrition prove to be a modifiable risk factor for FASD.

Another study will take place in Moscow, this one under the direction of Dr. Sarah Mattson. This is an extension of a pilot project ongoing in the orphanages and boarding schools in Moscow over the last two years. A complementary study will be done in San Diego, CA. Both sites will utilize the procedures suggested by the neurobehavioral core and comparisons both within and between the sites will be conducted. The high rates of FASD in the institutions in Moscow, the fact that all of the children live in similar environments, and that IQ can easily be controlled make Moscow an ideal location for this work. Paralleling this work with data collected in San Diego allows for the cross-cultural comparisons and helps to evaluate environmental factors and overall cognitive functioning in FASD. The specific aims of this study are to determine the relationship between neuropsychological functioning and general intellectual functioning in children with fetal alcohol spectrum disorder (FASD), by comparing children with FASD and children with a range of intellectual ability. Another aim of the project is to examine the relationship between general intellectual and neuropsychological functioning in these children by comparing children with FASD and controls over a range of intellectual ability. These investigators will also examine the relationship between environmental factors and neuropsychological functioning in these children by comparing children with FASD and children with similar environmental influences. Finally, this project also involves brain imaging at both sites with the goal of correlating measures of brain structure, as suggested by the imaging core, with results of neuropsychological testing. The overarching goals of this project are to compare the performance of children with FASD across cultures, environments, and overall ability levels to determine whether a specific pattern of functioning or behavioral phenotype exists. By incorporating, the imaging studies at both sites, which will be analyzed by the Imaging Core, we will gain a better understanding of brain-behavior relationships in these children.

In a follow-up investigation to previous work, Dr. Sandra Jacobson will oversee a project in Cape Town, South Africa. Dr. Jacobson and her collaborators previously found that prenatal alcohol exposure was related to poorer performance on two innovative infant assessments: a numerosity test, which assesses magnitude representation, a precursor of arithmetic that has been linked to inferior parietal function, and the A-not-B test, an early precursor of executive function (EF). Specific arithmetic and EF deficits have been noted in other studies of FASD. They are now proposing to follow up this cohort at 4 and 6 years of age. Their aims are to administer new tests of arithmetic, EF, and attention based on the contemporary models derived from event-related potential (ERP) and imaging studies, to determine which elements of these domains are most specifically related to fetal alcohol exposure and to assess the predictive validity of infant numerosity and A-not-B in relation to 6-year cognitive and attention performance. Importantly, these investigators have been conducting this study prospectively, so that they have excellent data on drinking during pregnancy to validate those measures.

Another study is also planned for South Africa, under the direction of Dr. P.W. Kodituwakku. This is an intervention study, but importantly will also provide information about the general neurobehavioral profile of children with FASD, through the preintervention testing. This project will test the efficacy of three intervention methods in the remediation of specific behavioral and learning problems in children with FASD. The specific aims are to determine the degree to which: 1) cognitive control therapy improves academic skills and behavior in alcohol-exposed children; 2) family interventions and environmental modifications in the classroom improve academic skills and behavior of alcohol-exposed children; 3) specific speech/language interventions improve academic skills and behavior of alcohol-exposed children; 4) the changes in self-efficacy, depression, and meta-cognitive skills, contribute to the efficacy of the above treatment methods. It is important to realize that almost nothing is known about effective interventions in FASD children and this study will be one of the first to conduct an in-school remediation effort.

Dr. May will oversee a project that will take place in both South Africa and in the United States. This study will rely heavily on the Neurobehavioral Core and again will assist in defining those behaviors that help to differentiate FASD from other disorders. The Specific Aims of this project are to assess cognitive-emotional functioning in children diagnosed with FASD from a community in South Africa and a number of American Indian reservations in the Northern Plains States. Importantly, a specific statistical model of neurocognitive functioning will be tested with the aim of further elucidating cognitive dysfunction in alcohol-affected children. Over 150 children with FASD will be tested in South Africa and over 100 cases are available through the University of New Mexico. Again, the data gathered through the core test battery will be combined with those collected by other participants in the international collaborative project (e.g. Russia, Finland, Italy, and other various sites in the US) to create a large data base.

Another US site will study FASD in Atlanta, GA and be under the direction of Dr. Claire Coles. This population represents a diverse population that is characteristic of the Atlanta Metropolitan area. In addition to the neurobehavioral test proposed by the Neurobehavioral Core, all children will also receive a psychophysiological test to examine deficits in attentional regulation and behavior and these will be related to more conventional measures of attention and learning. Because of increasing evidence linking prenatal alcohol exposure to deficits in white matter, a subsample of children with FAS will undergo brain imaging and particular attention will be paid to the relationship between neurobehavioral deficits and white matter integrity using diffusion tensor imaging (DTI). These examinations should contribute to the description of neurobehavioral deficits in children with FASD as well as illuminate the neurophysiological correlates of such deficits.

The last international site involved with a U01 project will occur in Finland and be under the direction of Dr. Ilona Autti-Rämö. She is a specialist in Pediatric Neurology at the Hospital for Children and Adolescents/Neurology, Helsinki University Hospital. FASD research has been ongoing in Finland for over 15 years and we were able to attract this excellent group of researchers to our consortium. Four separate studies will be conducted on adolescents and young adults that have earlier been assigned diagnoses of FASD. As this project involves the oldest group of subjects in the consortium, the first study will examine the educational and vocational status as well as present problems being faced by these young adults. Subjects will then undergo thorough neuropsychological assessments using, in part, the Neurobehavioral Core battery. In addition, magnetic resonance imaging (MRI) and spectroscopy (MRS)

will be carried out on part of these subjects in order to obtain further information on the neurobiological pathology underlying impairments specific to this clinical syndrome. Finally, an intervention study is planned. An extensive neuropsychological treatment program based on the results from neuropsychological assessments will be conducted for a 2-year period. The program aims at training executive functions, verbal and social skills.

Pilot projects also allow access to potentially new sites. FASD has not been studied in the Ukraine, but this is a population in which there is substantial risky drinking, prenatal access to patients is reasonable, and the facilities for research collaborations are in place. In Italy, there is an interest in FASD and it provides a site where the pattern of drinking may be different than that at other sites in the consortium. Findings from a recently completed NIAAA contract in Buffalo, NY suggests that this group has the capability to engage area physicians and generate referrals of affected patients who would be available for further study. Also, the prevalence rates of FAS are high in Buffalo, compared to other areas. The Buffalo pilot project capitalizes on these resources to ascertain an ethnically diverse group of subjects who will undergo 3D facial imaging in order to compare and assess the diagnostic sensitivity and specificity of this modality in patients with FAS and similar disorders (e.g., Williams syndrome) in African American and Caucasian American populations. Recently published work using MRI to detect individuals with FASD has led to a pilot project to develop an ultrasound protocol for detecting newborns with prenatal brain damage from alcohol. If this project is successful, such a protocol could be instituted in collaboration with projects ongoing in Ukraine, South Africa, and other CIFASD sites, to carry out a full neonatal FASD detection study in a large sample (involving dysmorphology and later neurodevelopment).

The basic science group of the FASD consortium comprises a highly integrated group of studies that address the pathogenesis and prevention of FASD. The presence of a basic science group that is focused on the development of therapies will inform the activities of other components of the FASD consortium. As the consortium matures, therapeutic agents developed by the basic science group can be tested in well-characterized populations of women at high risk of bearing children with FASD. Bringing therapeutic or preventative agents to clinical trial is a long-term goal that will not likely be met during the first five years of funding. However, by improving the clinical characterization of FASD and attempting prevention and intervention measures, the consortium will lay the groundwork and develop the infrastructure for testing of novel therapeutic agents in international populations. With its focus on the pathogenesis of FASD, the basic science group will also provide guidance for consortium studies that concern the structural and functional consequences of prenatal ethanol exposure.

While small, the basic science group has a predominant focus on the development of therapeutic agents that might prevent or mitigate FASD. The collaboration of four research groups centers on the recent discovery of alcohols and peptides that block discrete molecular actions of ethanol and prevent ethanol teratogenesis. Work performed in one of the consortium laboratories has demonstrated that 1-octanol and NAPVSIPQ (NAP) prevent ethanol inhibition of L1 adhesion (ethanol antagonism) (Wilkemeyer et al. 2002). Although NAP was developed as a neuroprotective agent, its antagonism of ethanol effects on L1 correlates strongly with NAP prevention of ethanol-induced dysmorphology in mouse whole embryo culture (Wilkemeyer et al.). An alanine substitution analysis of NAP has revealed different structure activity relations for ethanol antagonism and neuroprotection. Specific alanine substitutions of NAP have been identified that selectively block ethanol effects on L1 or abolish neuroprotection (Wilkemeyer et al.). These NAP mutations will be employed in various model systems to determine whether neuroprotection or ethanol antagonism is more important for protecting against ethanol teratogenesis. Preliminary data in two of the consortium laboratories have established the therapeutic efficacy of NAP in different models of ethanol teratogenesis.

An important goal of the basic science group is the development of medications that might mitigate or prevent the development of FASD. The administration of drugs to pregnant woman has potential hazards. One must bear in mind that many medications are taken safely during pregnancy to prevent conditions that are more dangerous to the mother and the fetus than the medication itself. In populations where FAS has a prevalence of 4.6%, the failure to treat has real and tragic complications. It is realistic to consider matching medications with low risks of teratogenicity to populations where the risk of FAS is

extremely high. Moreover, a long-term goal of the basic science group would be the development of medication delivery systems that release an alcohol antagonist only in the presence of alcohol. This approach would limit exposure of the antagonist to the period of greatest potential benefit.

Although the proposed studies are written specifically for studies of L-NAP and its derivatives, the Aims reflect a general strategy that can be applied to any compound determined by the Basic Science Group to have promise as a potential therapeutic agent. A candidate can be screened relatively quickly for its ability to protect against acute alcohol-induced activation of caspase-3 (in Purkinje cells on PD 4 in this component or forebrain neurons on PD 7 in Zhou's component). Additional studies of promising candidate agents can determine whether they afford neuroprotection against binge alcohol exposure over more extended portions of the 3rd-trimester equivalent.

A second goal of the basic science group is to improve the understanding of the pathogenesis of FAS. Ethanol has multiple cellular targets in the nervous system; hence, it is not surprising that ethanol damages the fetus through a variety of mechanisms: oxidative injury, induction of apoptosis, suppression of neurogenesis, disruption of cell-cell interactions, and alterations in the release and signaling of growth factors, morphogens, and chemical messengers (Goodlett et al. 2001). Several drugs that block specific molecular actions of ethanol have been shown to prevent or mitigate ethanol teratogenesis in animal models (Chen et al. 2001; Spong et al. 2001; Wilkemeyer et al.), an unexpected finding, given the complex pathophysiology of FAS. Delineating the mechanism of action of these drugs would help to identify the most critical mechanisms that underlie ethanol teratogenesis. This knowledge will help guide clinical studies on the neurologic and behavioral complications of prenatal ethanol exposure and may lead to new interventions.

We have contended (Goodlett 1999) that ***the next generation of animal model research should focus on three key areas relevant to human FASD***: **1)** identifying mechanisms of damage that can inform development of interventions to protect the conceptus; **2)** identifying therapeutic interventions or treatments, administered as early in development as feasible, to prevent or ameliorate the effects of prenatal alcohol-induced brain damage; and **3)** identifying sensitive indices of fetal alcohol exposure or damage to permit early detection and guide treatment. Progress toward these goals demands conceptual integration across different levels of analysis of the neurosciences spanning basic and clinical disciplines, as represented in this multidisciplinary consortium. For animal model studies to be most effective in identifying effective therapeutic agents to treat or prevent FASD, neurobehavioral endpoints must be chosen that can be directly related to similar endpoints in humans. The neural systems mediating the behavior must be relatively well defined and should be essential to the behavior both in the animal model and in humans. The neurobehavioral functions should also be suited for experimental assessment in animals and humans, and the neural systems and behaviors should be known to be a target of fetal alcohol exposure in humans.

Project 1 (Miller et al.) will attempt to characterize the structural basis for the action of molecules that prevent ethanol teratogenesis. Using photolabeling and mass spectroscopy, the investigators will ask whether there are distinct binding sites on the L1 cell adhesion molecule for ethanol and for drugs that block the effects of ethanol. The structural characterization of these sites will greatly facilitate the rational design of new therapeutic agents. Project 2 (Goodlett et al.) will study whether NAP and selected NAP derivatives prevent Purkinje cell death in a well-characterized mouse model of third-trimester equivalent binge drinking. Loss of Purkinje cells will be correlated with impairment of the eyeblink conditioned reflex. Project 3 (Zhou et al.) will follow up on exciting preliminary data showing that NAP and SAL, a related peptide, prevent ethanol-induced disruption of the development of brain serotonergic systems. Effects of NAP and NAP mutants will be examined at two development periods – first and third trimester equivalents – and in two brain regions – the serotonergic brainstem neurons and the hippocampus. Project 4 is highly integrated with Project 2. Both focus on the effects of third trimester ethanol exposure on cerebellar development and the prevention of ethanol effects using NAP. However, in Project 4 (Cudd et al.), a sheep model of ethanol exposure will permit the evaluation of ethanol effects over more discrete periods of development, with greater attention to maternal-fetal interactions. Importantly, Projects 2 and 4 will develop in parallel eyeblink classical conditioning as a test for disruption by ethanol of specific cerebellar, brainstem, and hippocampal circuits.

In addition to studying basic mechanisms of FASD and developing potential pharmacologic interventions, the basic science group will be studying psychophysiologic tests of brain dysfunction that will be applicable for early detection of infants with FASD. The investigators will develop an eye blink reflex test in sheep to correlate with data obtained in rats. The systematic experimental analysis of classical eyeblink conditioning over the last half-century has provided neuroscientists with a powerful empirical tool to analyze the function of neural circuits mediating one form of associative learning. One important advantage of eyeblink conditioning is that the same procedure can be used with both human and animal subjects (Woodruff-Pak et al. 2000a; Woodruff-Pak et al. 2000b). Indeed the procedure is able to distinguish human populations that differ along important cognitive and neurological dimensions. These include children and adults with dyslexia (Coffin et al. 2000), mental retardation (Ohlrich et al. 1968), temporal lobe amnesia (Clark et al. 1998; McGlinchey-Berroth et al. 1997), and autism (Sears et al. 1994; Sears et al. 2000). Investigators from the basic science group are engaged in studies of eyeblink conditioning in human infants as young as 5-6 months of age (Ivkovich et al. 2000)) and have found differences between high-risk, very-low-birth-weight infants and normal infants at this age with this procedure (Herbert et al. (submitted, pending EPA internal review)). As the animal-model research progresses and assessment and intervention strategies are more fully developed, there is a very real possibility that these strategies could be tried on infants and children at risk for FASD.

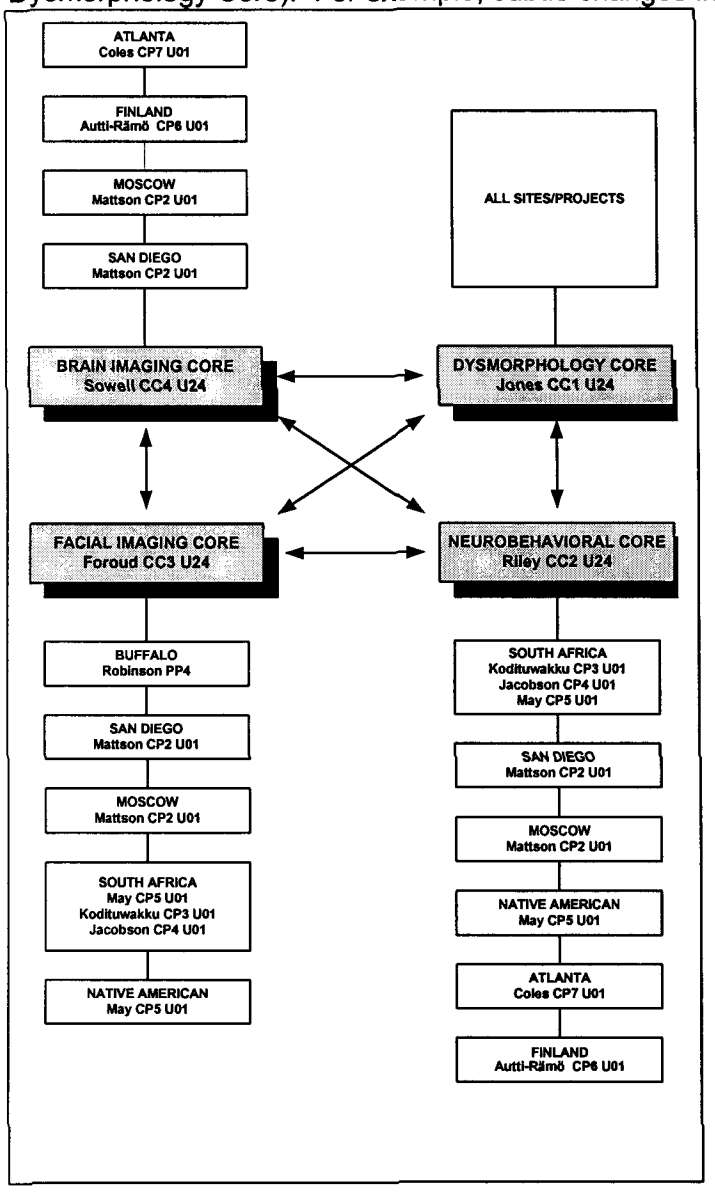
Investigators from this basic science group have all communicated with each other extensively over the past year concerning the proposed experiments. Collaborations among three of the laboratories were planned during the past two meetings of the Research Society on Alcoholism. The RFA for the FASD Consortium provided an impetus and potential funding for carrying out these collaborations. Each of the investigators in the basic science group represents a well-established, funded research program for studying the pathogenesis and prevention of FASD. The projects selected by each group for the FASD Consortium are new for each laboratory and relate closely to each other. The resources and infrastructure of these established research programs will be available to facilitate the collaborations within the basic science group. All members of the basic science group have also been involved in collaborative studies that span a range of disciplines related to FASD. This network of collaborators will serve as an additional resource for all components of the FASD consortium.

Communication among members of the basic science group will be facilitated through the use of E-mail, web-based data collection, and meetings. A modest travel budget is requested to permit representatives of each laboratory to meet in person to present data and plan future experiments. Two meetings will take place annually in Indianapolis, site of two of the laboratories, and at the annual meeting of the Research Society on Alcoholism. As Scientific Director and Co-chair of the Steering Committee, Dr. Charness will meet with representatives from all components of the consortium. These meetings will provide for integration of findings from the basic science group into the future plans of each component of the consortium.

IV. Additional information about collaboration among components of the CIFASD and recruitment of investigators not previously active in the alcohol field.

The basic structure and collaboration between clinical projects and cores is shown in the next figure. The Dysmorphology Core will interact with all of the other sites throughout the life of this Consortium to ensure that all projects are utilizing the same diagnostic criteria. We believe this is imperative if we are to better understand the range of outcomes following prenatal alcohol exposure. The Neurobehavioral Core will be interacting with each site where any behavioral assessments are being conducted (all sites, with the exception of some of the pilot projects). It will provide guidance as to the type of tests that should be administered so that a behavioral phenotype(s) can emerge. Directly linking to these cores is the Facial Imaging Core. We plan on using state of the art 3D imaging techniques and facial recognition software to discern the physical features that may be indicative of prenatal alcohol exposure. This Core will start with a few key sites and then expand to other sites. The Brain Imaging Core will interact with several of the sites. Imaging is proposed in San Diego, Los Angeles (through a separate project to Dr. Sowell), Moscow, and Finland and there is hope of obtaining imaging data from other sites as the consortium matures. The interaction of the Brain Imaging Core and the Neurobehavioral Core is an obvious one, as the behavioral changes are rooted in changes in brain. We also believe that the Brain

Imaging Core and the Facial Imaging and Dysmorphology Cores will interrelate. It is hoped that the detailed analysis of the face will act as a window into the brain, and that certain alterations in facial dysmorphology will correlate with changes in brain structure or function (see discussion in Dysmorphology Core). For example, subtle changes in facial midline structures might be related to alterations in brain midline structures (e.g. corpus callosum – a brain structure known to be affected by prenatal alcohol exposure). The Brain Imaging Core is envisioned as growing as the capability to add imaging to other sites, or to have new sites enter the Consortium becomes a reality. As stated above, all of the sites collecting neurobehavioral data will be interacting, as they obtain similar dependent measures within their projects.



The Brain Imaging Core has recruited Dr. David Shattuck, a highly talented computer scientist, into the study of FASD as a result of this proposal. Similarly, in the Atlanta project, Dr. Xiaoping Hu, will now be joining the FASD investigators. Dr. Hu's group recently moved to Emory from the University of Minnesota where they worked extensively on high field MRI, particularly its application to neuroimaging. In South Africa, three senior researchers who have not previously been active in fetal alcohol research are being added to this collaboration. Dr. Stanilas Dehaene, Institute de la Santé et de la Recherche Médicale, Paris, an internationally renowned cognitive neuroscientist; Dr. Charles Nelson, University of Minnesota, a developmental psychologist with expertise in ERP assessment of infants and children; and Dr. Nancy Jordan, University of Delaware, a cognitive psychologist with expertise in assessing precursors of arithmetic in young children. Dr. Chambers has recruited Carl Keen, Ph.D., Professor and Chairman of the Department of Nutrition at the University of California, Davis. He is an internationally recognized authority in his field, and an expert on the nutritional aspects of teratogenesis. Andrew D. Hull, M.D., Assistant Professor of Reproductive Medicine at the University of California, San Diego, has also been recruited to this Consortium. He devotes a substantial portion of his practice and teaching activities to the treatment of pregnant drug and alcohol abusing women. With over 15 publications related to prenatal diagnosis in the last three years, he brings his considerable expertise in two-and three-dimensional ultrasound to the proposed pilot project in Ukraine.

The CIFASD provides the opportunity to bring these scientists to the field of FASD studies and to provide experience in this area of research to their students and colleagues.

V. Institutional and Other Commitments to Overall Budget of Consortium

Several of the Institutions involved in this Consortium have provided resources for the development and/or maintenance of the Consortium (See supporting letters). San Diego State University has provided some release time for the PI to prepare the application. They also committed $20,000 to the CBT for resources pertaining to the research mission of the consortium (see attached letter). Indiana University

has provided all of the necessary facilities to obtain the pilot data related to the 3D facial imaging Core and thanks to funding from Indiana University, the State of Indiana, and the Lilly Endowment, Inc., Indiana University is contributing all of the computing resources required for the Consortium for Data Repository, as well as the statistical consulting, as part of its institutional commitment. It is difficult to gauge the value of this commitment in advance. However, it is expected that this commitment will be valued at a minimum of $100,000, and could feasibly reach a value of $500,000. Wayne State University School of Medicine has provided Joseph Young, Sr. funds from the State of Michigan to help supplement the prenatal alcohol exposure research in Dr. Jacobson's laboratory. Furthermore, the University of California, San Diego has provided release time for Drs. Jones, Chambers and Hull, (Dr. Jones on 3 one-week occasions – Drs. Chambers and Hull on 1 one-week occasion) for preliminary training of ultrasonographers, pediatricians and individuals to document alcohol consumption during pregnancy in Ukraine. All the consultants are contributing to the Moscow and Ukraine projects for nominal fees because they are highly interested in the projects. UCSD is donating existing software in the United States for both the Moscow and Ukraine projects. In the Ukraine Pilot Project, computer hardware and space are being donated by UCSD. Dr. Keen is receiving a donation of the vitamin supplements for the study in the Moscow Region. Finally Dr. Wertelecki is provided release time by the University of South Alabama to volunteer his time in the Ukraine Pilot Project and Drs. Jones and Chambers are also provided release time for this purpose. The Marcus Institute in Atlanta has provided resources and staff support for research efforts to be carried out in the FAS Clinic at that site. For the current proposal, they have agreed to act as a research site in collaboration with Emory University and to negotiate overhead expenses with that Institution rather than to include them in the budget as a subcontract. Dr. Coles and other professionals have been provided with release time by Emory University and the Marcus Institute to prepare these applications. In preparing pilot studies for the DTI procedures that are proposed, the Biomedical Imaging Technology Center provided time in the 3T magnet from their own funds. Approximately $250,000 has been appropriated by the Italian government for help in conducting the project proposed by Dr May. These funds support the field activities including personnel, logistical support, and ongoing professional research activities. In addition, Dr. Mattson has negotiated reduced rates for testing materials to be used in the neuropsychology core and hopes to negotiate donations of testing materials for use in the international sites. The sites all have access to testing facilities, equipment, and materials and to facilitate the conduct of the neurobehavioral core. The Laboratory of Neuro Imaging at UCLA is donating all of its existing brain image analysis software and access to all computing resources. Dr. Sowell has obtained funding from another source (NIDA DA015878) to recruit and conduct brain imaging studies on FASD children in the Los Angeles area. These brain imaging data will be added to the Consortium project.

VI. Structure and Organization of the Administrative Coordinating Core

Overview of the Core:

Given the diversity of the projects within this consortium, the primary goal of the Administrative Core is to provide an infrastructure that will allow effective communication between the various cores, components, and projects and to ensure the overall success of the consortium. Since the effectiveness of this consortium will rest in large part on the input and advice of the Steering Committee, a major role of the Administrative Core will be to provide administrative support to the Steering Committee. This will be accomplished by providing progress reports of the individual projects and collectively, progress towards the goals of the consortium to the Steering Committee on a regular basis. The regular meetings of the Steering Committee, as well as the meetings of the Science Advisory Board, and the annual meeting of the Participating Investigators will be arranged by the Administrative Core. In addition the Administrative Core will coordinate with the Informatics Core to ensure that communication within the projects is effective. It will also generate reports to all of the projects and ensure the dissemination of information to researchers, as well as to groups and individuals with an interest in FASD.

Organizational Structure:

The Administrative Core provides support to the Steering Committee and to the consortium as a whole.

Roles of the Core Personnel:

1. Director. Dr. Edward P. Riley will serve as the Principal Investigator of this consortium and as outlined in the RFA, as the Director of the Administrative Core. Dr. Riley is allocating 35% of his time towards meeting the goals of this consortium and he is well qualified to serve in this capacity for a variety of reasons. Dr. Riley has been a Professor of Psychology and the Director of the Center for Behavioral Teratology (CBT) at San Diego State University, the host institution, since 1988. The Department of Psychology is located in the College of Sciences and the Center for Behavioral Teratology is a University-wide research center. He has a broad perspective on FASD and currently conducts both animal and human studies aimed at a number of questions surrounding FASD. He presently chairs the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect, and Co-Chairs with Dr. Faye Calhoun, the Steering Committee of the SAMSHA sponsored FAS Center for Excellence. Both of these are national committees with goals to enhance the prevention and treatment of FASD and it provides Dr. Riley with access to current policies related to prenatal alcohol exposure. Dr. Riley has over 175 publications, most relating to the effects of prenatal alcohol exposure on brain and behavior and his work has involved both animal models as well as clinic populations of children with FASD. He has been recognized for his work in this area and is a recipient of the Henry Rosett Award for Outstanding Leadership and Research in FAS. He has also served as the President of the Research Society on Alcoholism, and as an Associate Editor of Alcoholism: Clinical and Experimental Research and the Journal of Studies on Alcohol. He is currently on the Board of Directors of ISBRA.

As the Director of the CBT, Dr. Riley has gained experience in integrating various projects, and in setting objectives and goals. The CBT has grown tremendously in the last few years, and now has grants totaling over $1,000,000 annually. In addition, he has experience in establishing and coordinating various projects such as his multidisciplinary R01, Behavioral, MRI and EEG effects of prenatal alcohol exposure, which involves five research sites. His recent efforts involve bringing together researchers engaged in neurobehavioral research on FAS from four laboratories to share data related to the behavioral teratogenic effects of ethanol. He also has experience in international collaborations, having begun projects in Moscow, Russia and most recently Helsinki, Finland. He also has organized two international meetings, in Spain and France, on FAS and he has interacted professionally with most of the members of this consortium and published with several of them.

As the Director of a University-wide Center, Dr. Riley is in a position to negotiate with the Vice President for Research at SDSU regarding matters related to space and resource allocation. Furthermore, he has an excellent rapport with the SDSU Foundation, being one of the most active PI's on the SDSU Campus.

As the PI of this grant, Dr. Riley will

1. Oversee the functioning of the consortium by providing scientific and administrative leadership
2. Act as a go-between for the Administrative Core, the Steering Committee, and the Science Advisory Board
3. Monitor the Cores and individual research projects for progress
4. Facilitate the interaction of the consortium scientists
5. Oversee the administration of the Pilot Project Component
6. Provide a mechanism for the evaluation of individual and core projects
7. Facilitate the recruitment of new scientists and new technology into the consortium
8. Be responsible for the dissemination of new data arising from the consortium
9. Act as a liaison between parent groups, advocates, and the consortium by maintaining interactions with these various groups.

2. Scientific Director of the Steering Committee. Dr. Michael Charness was chosen as the Scientific Director of the Steering Committee because of his unique background as a basic scientist and a clinician. Dr. Charness has trained in psychology, neurology and neuroscience. His basic research uses fundamental techniques in pharmacology, cell biology and molecular biology, and he has also been involved in human studies using structural and functional imaging. Dr. Charness is currently Chief of Neurology, VA Boston Healthcare System, Associate Chief of Neurology, Brigham and Women's Hospital and Associate Professor Neurology at Harvard Medical School. He is Board certified in both

Neurology and Internal Medicine. He is a recipient of the Frank Seixas Award from the Research Society on Alcoholism and serves on the Board of Directors for RSA and ISBRA. He has a long history of basic research in alcohol and his interests include mechanisms of alcohol neurotoxicity; development of alcohol antagonists; fetal alcohol syndrome; and the neurological complications of alcoholism.

3. Administrative Specialist. Dr. Jennifer Thomas will serve as a part-time Administrative Specialist. Dr. Thomas has extensive experience in the fetal alcohol research area and will assist the PI and the Scientific Director, Dr. Charness in preparing meeting materials and preparing drafts of reports and press releases. Because of her involvement in basic research she will be a key personnel in coordinating the Administrative Core with the basic science projects and in assisting Dr. Charness in his role as Scientific Director of the Steering Committee. She will play an active role in coordinating activities among all projects and will oversee interactions with the Informatics Core. She will also be responsible for keeping PIs updated on new findings that might be of interest to consortium participants. She will also assist in providing library resources and internet research to all consortium investigators as needed.

4. Administrative Assistant. The Administrative Core is requesting a full-time Administrative Assistant. Ms. Chay Pagdilao has been serving as an Administrative Specialist in the Center for Behavioral Teratology for the past two years and has become knowledgeable about the effects of prenatal alcohol exposure. Currently her main duties include but are not limited to, office management, proof reading of documents, creating documents in Word, Excel, Power Point, and SmartDraw (charting program), assisting with grant preparation, reprint requests, maintaining updated information in various files (vitas, requisitions, personnel, etc.), and some supervision of students. She coordinates and manages the following: accounts receivable and payable, travel arrangements and reimbursement, submitting and follow-up of requisitions, assisting with personnel recruiting, payroll/timesheets, data analysis and reporting, processing mail, filing, and organization.

Prior to the CBT, Ms. Pagdilao worked for the County of San Bernardino as a Secretary and Fiscal Clerk, and as a Lead Account Representative for Arrowhead Orthopedics. In summary, her responsibilities included primary support to various managers, client service, office management, supervision, developed policy and procedure, preparation for various federal agency visits, managed personnel and client information, and developed, drafted, proofed, and transcribed various documents. She also coordinated schedules, travel arrangements, data analysis and reporting, fiscal reporting, payroll, personnel recruiting, meetings and events planning, supplies and equipment requisitions, internal data audits, patient satisfaction surveys, and department safety. These experiences make her suited for this current position.

Ms. Pagdilao will act as a resource to the consortium and all of the participants. Specifically, she will act as the go-between in coordinating efforts between the consortium participants. She will be responsible for maintaining records of publications, help to maintain the website related to the research finding of the all study participants. She will also assist with data archiving, preparing notes for and taking minutes of the meetings. She will have a part-time student assistant to assist her with her administrative duties.

5. Student help. Part-time person to assist Administrative Assistant with the day-to-day operation of the Consortium.

Facilities

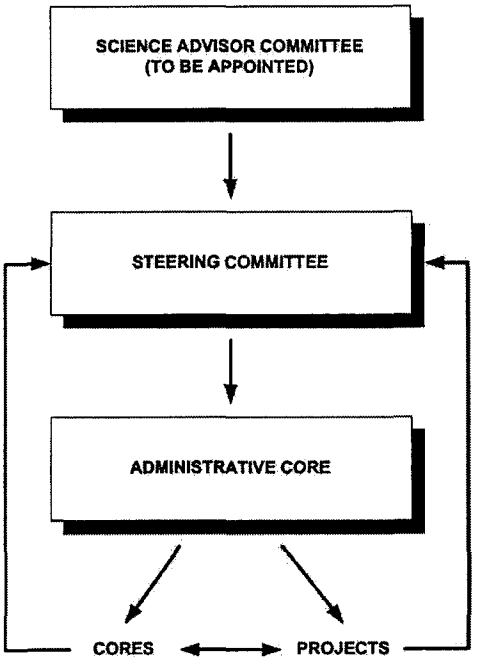
The Administrative Core will be housed in the offices of the Center for Behavioral Teratology, San Diego State University. Currently, the CBT occupies half of the second floor of 6363 Alvarado Ct., a building devoted to research projects within the Department of Psychology. This building houses most of the clinical psychology faculty at SDSU and the Psychology Department Clinic. The CBT occupies almost 5000 sq. ft. of space in the Alvarado Ct. Building and office space is provided for the PI, the Administrative Assistant, and any additional staff required for the Administrative Core.

Communication: One of the objectives of the Administrative core is to allow effective communication between the various cores and projects. Furthermore, the members of this consortium strongly believe that we need to make our results known to the broader public audience and communicating our findings to this audience will be an essential part of the Administrative Core.

Overall Communication. Communication regarding the administration of the program will flow through the Administrative Core. It will be responsible for ensuring that the Steering Committee members are informed about the progress and problems faced by the individual cores and projects in a timely fashion. It is envisioned that the Steering Committee will meet twice per year and have monthly conference calls. The Administrative Core will be responsible for arranging these meetings and calls, and ensure that the members have the appropriate information relevant to the cores and projects prior to the meeting.

Maintenance of Consortium website. The Administrative Core will take responsibility for establishing a consortium website to provide general information about the program. Links to participating scientists will be provided where possible. New findings and publications or abstracts of publications will be provided in an easy-to read format in the hopes of disseminating this information to the general public. Access to our scientific papers will be provided as allowed by copyright law. We will also ask that our website be linked to various other websites concerning FASD. As the Consortium is viewed as a dynamic entity and attempt to recruit additional projects to the consortium, the website will also contain applications by which investigators can apply to join the consortium. There will also be forms for request of services that the PI's of the various components can utilize to allow for better utilization of shared resources (e.g. 3D cameras, imaging services, etc).

Dissemination of program information – In coordination with the Informatics Core the Administrative Core will be responsible for all interim reports and the Annual Report to the Steering Committee, the Science Advisory Board, and to NIAAA.



Interface between participating investigators and the Steering Committee. Each participating investigator will be assigned a member of the Steering Committee as their ombudsman and advocate. In this way, each project PI staff will have direct access to the Steering Committee, the group responsible for the scientific goals of the consortium. Each PI will therefore be represented at the monthly meetings of the Steering Committee via teleconferencing, and at the two annual meetings of the Steering Committee. This assignment will be made at the initial meeting of the Steering Committee. In addition, each component will be assigned to an administrative unit (e.g. clinical group, neurobehavioral group) and a person appointed to represent that unit. This should provide for some overlap in representation at the Steering Committee meeting.

Meetings

Given the integrative nature of the projects proposed here, it is imperative that the group meet on a regular basis. The Administrative Core will be responsible for arranging these meetings.

1. Participating investigators meeting. This will be held annually, principally at the RSA meeting, since most of the consortium participants typically attend this meeting. At the participating investigators meeting, the consortium scientists will be expected to provide annual updates to their projects and to interact with the Science Advisory Panel and the Steering Committee to help shape priorities for the upcoming year. Additionally, a few scientists from fields outside of the fetal alcohol research community will be invited to attend, so that new investigators can contribute to the discussion and hopefully be enticed to consider submitting an application to the consortium.

2. Steering Committee meetings. Meetings of the Steering Committee will be held twice per year. It is envisioned that one of the meetings will be held in conjunction with the RSA meeting and the other in Washington, DC (a consortium requirement). Individuals who cannot attend physically will be expected to participate via teleconferencing.

3. Scientific Advisory Panel. A meeting of the Scientific Advisory Panel will be held at least once per year in conjunction with one of the meetings of the Steering Committee. This joint meeting will occur just prior to the Steering Committee meeting and the Participating Investigators meeting (see below), so that the comments, suggestions, of the Advisory Panel can be communicated to the larger group in a timely fashion. We will arrange this meeting in conjunction with RSA, as this will allow for the Panel members to see the progress of individual projects in the context of the whole consortium.

Administrative Management Plan

A. Organizational Structure:

The Steering Committee is the administrative branch around which the Consortium is organized. It serves as the governing body of the project and is chaired by the Principal Investigator. Support is provided by the Administrative Core. As detailed above for the Scientific Organization of the project, the Steering Committee oversees and tracks the progress of the Core Resources and the participating investigators. The Scientific Advisory Committee of outside experts will convene annually at a meeting of all participating investigators to keep appraised of the progress and make recommendation to the Steering Committee and NIAAA.

1. Steering committee: The Steering Committee currently consists of the Principal Investigator and six additional participating investigators who are collectively well known for their scientific and organizational leadership in this field. Each of them has also assumed other responsibilities in the program (see table). This is the current composition of the Steering Committee, the advising group during the preparation of this application. However, the composition may change slightly to get representation from the Informatics Core, which we feel is essential. Our goal, however, in putting together the Steering Committee is to ensure that Core Resources and Subgroups have representation on the Steering Committee, either through direct representation or through an assigned member of the Steering Committee. To ensure this, members will be appointed in consultation with the Science Advisory Panel, as needed to ensure that each major component of the project is represented. The Steering Committee has substantial responsibilities for oversight and integration of the program covering both Administrative Management and Program Management. Perhaps the most important role of the Steering Committee is the review of scientific progress of the individual components of the consortium. Furthermore, the Steering Committee will oversee the annual review of the budget and help with the redistribution of resources if possible. Finally, the Steering Committee will be responsible for oversight of Core resources, and prioritize the utilization of these resources.

Table 1. Composition of the Current Steering Committee

Name/Institution	Role in Program
Edward Riley, Ph.D. San Diego State University San Diego, CA	PI – Director Administrative Core Steering Committee Chair Behavioral Core and Pilot Projects PI Co-PI San Diego, Moscow Projects
Michael Charness, MD Harvard Medical School VA Medical Center West Roxbury, MA	Scientific Director and Co-Chair, Steering Committee Director, Basic Science Group Pilot project 1.
Tatiana Foroud, Ph.D. Indiana University Indianapolis, IN	PI 3D imaging Core
Sandra Jacobson, Ph.D. Wayne State University Detroit, MI	PI South African Project Neurobehavioral Core

Kenneth Lyons Jones, MD University of California, San Diego San Diego, CA	PI Dysmorphology Core Co-PI Moscow Neonatal Project PI Ukraine Pilot Project
Sarah Mattson, Ph.D. San Diego State University San Diego, CA	PI San Diego Moscow Project Neurobehavioral Core
Philip May, Ph.D. University of New Mexico Albuquerque, NM	PI South African/Native American Project PI Italian Pilot Project

2. Principal Investigator-Consortium Coordinator: The Principal Investigator, Dr. Edward Riley has been actively involved in alcohol research since 1974. He currently is Professor in the Department of Psychology, San Diego State University and Director of the Center for Behavioral Teratology. The Consortium Coordinator will chair the Steering Committee and direct the Administrative Core. He will oversee the research of the Consortium with the help of the Co-Chair of the Steering Committee/Scientific Director of the Steering Committee, Dr. Michael Charness.

3. Scientific Director and Co-Chair of the Steering Committee: The Scientific Director and Co-chair of the Steering Committee is Dr. Michael Charness. Dr. Charness has extensive experience in both basic and clinical research. He is an outstanding scientist and has the ability to interact with both the clinicians and basic scientists. Dr. Charness is currently Chief of Neurology, VA Boston Healthcare System, Associate Chief of Neurology, Brigham and Women's Hospital and Associate Professor Neurology at Harvard Medical School.

Dr. Charness will be responsible for overseeing and supervising the research of the Consortium to coordinate scientific goals and priorities with maximum efficiency with an aim of avoiding overlap and unnecessary duplication. Dr. Charness as Co-Chair of the Steering Committee, will help oversee the Steering Committee meetings and replace Dr. Riley at these meetings if for some reason he is unable to attend.

4. Administrative Core: Day to day operations of the Consortium will be left to the PI of the Administrative Core, Dr. Edward Riley. He will be responsible for making arrangements for all meetings and deciding on the agenda for the monthly conference calls and meetings. As PI, Dr. Riley will also communicate with NIAAA on any business related to the scientific aspects of the projects. In conjunction with the Steering Committee and the Informatics Core, he will disseminate information about the progress of the various projects to the consortium participants. Similarly, as part of the mission of the consortium is to bring the information obtained by the research effort to the attention of the general public, it will be his responsibility to make sure that dissemination of progress is made to as broad of audience as possible.

5. Informatics Core: The Informatics Core is integral to the performance of the consortium. It will be responsible for some data analysis and for maintaining the databases for the consortium. In conjunction with the other cores and projects, relational databases will be designed so that data obtained at the various sites is maintained in some systematic fashion. This will allow other investigators access to the information, and the data to be analyzed as a single set of data with site as a factor in any analysis. The Informatics core will be available for data consultation and for help in data analysis. This Core will also coordinate with the Administrative Core to prepare summary reports so that progress towards specific goals can be determined.

6. Core Scientific Resources: As stated above, each Core will have a member of the Steering Committee representing its interest, and it is the Steering Committee that will assist in the allocation of Core resources.

7. Participating Investigators and Subgroup Leaders: Again, as stated above, each participant will have an ombudsman on the Steering Committee to ensure an active and participatory style.

Community Impact:

It is viewed as imperative that findings from this consortium make their way into the public domain as quickly as possible, without compromising ethical standards of publications or scientific integrity. The Consortium will have a public website, which will contain information, papers, abstracts, etc. as progress towards the goals of the Consortium is made. Furthermore, other investigators will have access to the data collected by the consortium, through a public database. Data included in this database will have already been made public through publication or at meetings.

The Consortium, through the Administrative Core, will also maintain contact with various parent, advocacy, and professional organizations. For the last several years, Dr. Riley has participated in numerous trainings sessions of parents and professionals on the changes in brain and behavior that occur following prenatal alcohol exposure. He has an excellent rapport with these groups and will continue to actively be involved in their efforts (See attached letters). Other consortium participants also engage in these outreach efforts and the consortium will encourage and support such endeavors as much as possible. One possible mechanism is to produce a slide set covering all aspects of FASD. Utilizing Consortium personnel and outside experts, the consortium would like to produce a detailed Power Point presentation on FASD. Dr. Riley wrote the lecture series on FAS that is currently part of the RSA lecture series on alcohol. He has received numerous requests to use the slides contained in that lecture. However, the lecture series is only 25 slides and covers FASD in general. The consortium would hope to expand on this type of presentation and provide a number of lectures and slides that could be accessed by anyone.

IX. Program Management Plan of the Administrative Coordinating Core

The Steering Committee will be responsible for the oversight of the Consortium and will set priorities for the cores, allocate resources, review the progress by the cores and the various projects, review budgets and financials allocations, and develop a plan for the sharing and distribution of data and other intellectual property.

Setting Annual Priorities:

1. At the first meeting of the Steering Committee, the group will be asked to set research priorities for that year. This will consist of developing a set of priorities for the Cores, such as which sites should be visited first by the dysmorphologists, where the 3D camera project should be initiated, etc. This will be a serious task and will take into account the interrelationship between the various Cores and projects, the priorities set by the Steering Committee, and the needs and expectations of the participants.

2. Evaluations for Cores: The Steering Committee will evaluate the progress of each Core at its biannual meeting and if necessary during any of the monthly teleconferences. Additionally, requests for resources from any project regarding Core services or additional resources needed by the Cores will be discussed. Requests for resources must be fully justified and put in terms that are subject to adequate evaluation at subsequent meetings of the Steering Committee. The Steering Committee will also be responsible for any adjustment of services provided by the Cores to specific project based upon findings and progress of the projects.

Distribution of Resources:

1. The annual priorities for each Core will be posted on the consortium website so that each investigator is assured rapid and up-to-date information. Similarly, the Cores will list available resources on the website, so that specific projects can request these resources for allocated times. An example might be the allocation of the 3D camera resource, where specific times it was available might be listed, so that any site could request the services of this core.

2. Requesting resources: Following the initial allocation of Core Resources by the Steering Committee, any participating investigator could request Core Resources by completing a standard form posted on the website. The from will request standard information about how long a Core Resource will be required, the aim of the project that the resource will address, a brief description of the protocol for which the resource is requested, and any additional information that the PI feels justifies the need of the resource. The request will automatically be sent to the Consortium Coordinator, Scientific Director, and

Steering Committee (Administrative Core). The Scientific Director and the Consortium Coordinator will discuss the request and make a decision regarding the allocation of the resource. If it requires input from the Core, the PI on the Core project will also be consulted. The project PI will receive confirmation of the request, and following the monthly conference call of the Steering Committee a date for allocation of the resource will be made available to the PI.

3. Allocation of resources: The Core Director will evaluate requests for resources within a specific core, and in consultation with the Steering Committee, will decide when and how much of the Core facilities can be allocated to the project. For example, a project might request services of the dysmorphology core. The request would be made via the website and the Steering Committee along with the Core Director, Dr. Jones, would decide on the urgency of the request and when the requested service (e.g. dysmorphology screens at a particular site) could be provided. Decisions will be made in a timely fashion and the Core will do everything possible to honor the request in a designated time frame.

Review of progress:

1. Services provided: At the midyear meeting of the Steering Committee the Core Directors and participating investigators of research projects will provide the Steering Committee with a brief report of the status of their progress with respect to the goals set at the beginning of the year. Cores will be responsible for justifying the allocation of the resources and for not providing services requested by individual projects. Core directors and the PI of the various components will be required to provide a full progress report to the Consortium Coordinator during the year.

2. Effectiveness of Core Resources: The annual report will describe the activities and effectiveness of the core in the context of its role in the overall program. For example, for the 3D Camera Core, the report will detail the use of the camera, at which sites it was used, how many individuals were photographed, how many evaluated, and any findings in relation to the Dysmorphology Core.

3. Tracking progress towards specific aims: Tracking the overall progress of the individual projects and in the Core will be a function of the Administrative Core. Of course the Administrative Core will rely upon the Informatics Core in this regard. The Informatics Core will provide detailed information about the number of individuals assessed in each project.

4. Annual participating investigator meeting: Following submission of the progress reports, an annual meeting of all participating investigators will be held to update all investigators on progress within the project. Investigators will be looking for ways to achieve greater integration of projects, and to learn about priorities for the upcoming year. They can also make any suggestions at this time that they feel would benefit the operation of the consortium.

5. Role of the Scientific Advisory Committee: The Scientific Advisory Committee will be composed of internationally recognized experts in the fields comprising the scope of the current and planned research in the project. They are expected to provide an expert and objective review of the progress of the project, and make recommendations to the Steering Committee on both the program and the investigators. At a minimum they will be expected to attend the annual participating investigators meeting, and to meet with the Steering Committee to provide feedback and to obtain any additional information needed to evaluate the program. Following these meetings the Chair of the Advisory Committee will prepare an Annual Report of the Advisory Committee. The report will be expected to include an evaluation of the progress and quality of the research for each subgroup, an assessment on the effectiveness and/or productivity of the Participating Investigators, the Core Resources, and the Administrative functions of project. The Steering Committee will utilize the report of the Advisory Committee in its overall evaluation of the component parts of the project.

Review of budget and resource allocations:

1. Review of budgets for Cores: Soon after the participating investigators meeting and prior to the end of the fiscal year (anniversary date of the project funding), the Steering Committee will conduct a formal evaluation of each core resource and approve the budget for the coming year. The Steering Committee will use the progress reports submitted by the Cores and the individual projects from the participating

investigators, as well as the recommendations of the Advisory Committee in considering the allocation of resources.

Particular attention will be paid to progress relative to priorities. In the initial year some leeway will be given to the learning curve on the process of setting appropriate priorities and tracking progress using them. In subsequent years, not meeting service needs and lack of performance and the resulting negative impact on progress goals will be cause for concern. If a Core resource fails to meet its service requests, fails to provide resources to other Cores or participating investigators, or is underutilized by other Cores and participating investigators, there will be various remedies applied, including personnel changes, and/or requests to NIAAA for supplemental funding or other changes in the noncompeting application budgets.

2. Review of resource allocations: On an annual basis (or more frequently) the Steering Committee will review the list of resources allocated and determine whether or not each participating investigator is depositing data into the program database maintained by the Cores and the Informatics Core. If a participating investigator is non-compliant, an inquiry will be made as to why, and determine if the Informatics Core can provide assistance. If a participating investigator is consistently non-compliant with this important obligation, additional requests for resources will not be honored.

Decision and Conflicts:

While we certainly do not anticipate any conflicts as many of the PIs have worked together previously, plans have been made to address this concern. The Consortium Coordinator will obviously have the ultimate responsibility for any decisions, although he will rely on the Steering Committee and the Science Advisory Panel for direction. Decisions will be made based upon the input from these groups, in particular the Steering Committee, which serves as the governing body. The Scientific Director will deal with issues related to the research aims of the consortium and in the event of any conflicts between the members of the Steering Committee, a majority vote will be honored. As a further failsafe mechanism, those members of the Steering Committee voting in the minority can appeal decisions to the Science Advisory Panel for reconsideration.

Plan for data sharing and intellectual property.

1. We will rely on the use of our website as a means for data sharing and the transfer of information between the individual investigators. The Informatics Core will be responsible for collecting data from each of the Cores and creating a common database, which it will manage. Access to this database will be available to PIs that need the data, at least until the data are published, when we hope to make it more widely available to other investigators. The Cores will also maintain data for their respective projects. For example, for the neurobehavioral projects, it is expected that each of the sites will keep data collected at their individual site in their own database. They will also forward the information in a timely fashion to the Neurobehavioral Core, which will then act as a clearinghouse for the data. The Neurobehavioral Core in turn will forward the information to the Informatics Core, so that it will be available to investigators who require access. Access interfaces will be user friendly and intuitive as described in the Informatics Core. Program participants will have access to the appropriate sections of the database through the website, and the public will have access to the subset of information that has been publicly disclosed.

2. An annual progress report will be delivered to the investigators and to NIAAA within one month following the anniversary date of the project. Parts of the progress report will be confidential to individuals with a role in the consortium, while other parts will be posted on the public part of the website so that anyone can follow the progress of the Consortium.

3. Publications and Authorship: One of the roles of the Administrative Core will be to maintain a cumulative list of all publications by Participating Investigators that relate to the consortium. All of the participating investigators have agreed that the information gathered in this project should be publicly disclosed. Given that much of the data will be collected across sites, clear agreements about authorship will be obtained prior to the start of any collaborative ventures. We will use standard rules of authorship for publications.

4. All participants will be required to disclose to the Administrative Core any ties to profit making organizations that may benefit from any of the work of the Consortium. We do not see this as a problem, but we have met and discussed this so as to avoid any appearance of a conflict of interest. If instances do arise they will be dealt with by the Steering Committee who will make a recommendation on how to best handle it to the Administrative Core.

5. Disclosure of subject invention to NIAAA: All investigators will be required to inform the Administrative Core of any inventions that are disclosed to the grantee institution's patent department. The Administrative Core will log all patents and follow-up with NIAAA to ensure that the individual investigator disclosed this patent information to NIAAA. All of the investigators will be made aware in writing of the fact that NIAAA has to be notified of all patent related products within two months of disclosure to the appropriate office.

E. Human Subjects. The Administrative Core is not conducting any studies on its own, but is rather providing administrative support to the Consortium. However, it will ensure that each project has appropriate human subjects approval before any resources of the Consortium are allocated to that project. The Administrative Core will also maintain a file of all approvals issued to the individual projects.

F. Vertebrate Animals. Again, the Administrative Core is not conducting any research, rather, it coordinates the various projects, some of which involve vertebrates. The Administrative Core will ensure that appropriate approvals are in place for each project prior to the allocation of any Core resources and will maintain files of all approvals issued to the individual projects.

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