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.**

Diagnosis of the Fetal Alcohol Spectrum Disorder (FASD) is dependent on the identification of a pattern of malformation including alterations in growth and neurobehavioral development as well as a constellation of specific minor craniofacial anomalies. In that a neurobehavioral phenotype specific for prenatal alcohol exposure has not yet been identified, it is presently not possible to diagnose FASD in the absence of the clinical phenotype. 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 which will be used at all sites. In that this consortium will integrate investigators from different sites throughout the world, it is imperative to have a small core of individuals with extensive experience in evaluation of children prenatally exposed to alcohol responsible for diagnosis of FASD at all sites.

Identification of large numbers of children with FASD at various ages, each of whom has received a standardized clinical evaluation will provide the opportunity 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, the extent to which degrees of growth deficiency should be used to enhance specificity of diagnosis without loss of sensitivity, and will provide the opportunity to develop strategies to diagnose this disorder in the newborn period.

PERFORMANCE SITE(S) *(organization, city,* state)
Seattle, Washington
Moscow, Russia
Finland
Sweden
Rome, Italy
West Cape Province, South Africa
Ukraine
Atlanta, Georgia

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
Jones, Kenneth Lyons	University of California San Diego School of Medicine	Dysmorphology Core Director, Dysmorphologist
Del Campo, Miguel	Universidad Pompeu Fabra, Spain	Consultant
Hoyme, H. Eugene	Stanford University School of Medicine	Dysmorphologist
Robinson, Luther K.	State University of New York at Buffalo	Dysmorphologist
Strömland, Kerstin	Göteberg University, Sweden	Consultant

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

A. SPECIFIC AIMS:

Diagnosis of the Fetal Alcohol Syndrome (FAS) is dependent on documentation of the clinical phenotype in a child prenatally exposed to alcohol. Members of the Dysmorphology Core have been involved over the last 7 years with the establishment and execution of a protocol that has been used by them in South Africa and Russia to establish diagnosis of the disorder in large populations of children in those countries. The protocol involves the evaluation of large numbers of children by selected local physicians who have been trained by members of the Dysmorphology Core in diagnosis of FAS, followed by confirmation of their diagnosis in all documented or suspected cases by members of the Core. This methodology has provided the "gold standard" with respect to diagnosis without which any attempt to correlate neurobehavioral abnormalities with prenatal alcohol exposures in the two studies conducted in those countries would not have been possible.

In addition to the development and implementation of this protocol in South Africa and Russia, members of the Dysmorphology Core have been instrumental in the clinical delineation of FAS as well as studies involved with mechanisms involved in the development of the clinical phenotype of FAS.

We will build on this established record, continuing to provide quality assurance relative to the clinical diagnosis of FAS. Through analysis of the clinical data including that relating to growth and major and minor malformations from large numbers of affected children of various ages ascertained at the various clinical sites in the consortium, we will be able to establish more objective criteria for diagnosis of FAS. In addition, we will be able to document the full range of structural anomalies in children prenatally exposed to alcohol and in conjunction with the Neurobehavioral Core be able to determine clinical features that are most predictive of future problems with neurobehavioral development. In order to achieve these goals, we propose:

1. To insure consistency as well as accuracy in diagnosis of FASD at all project sites where children are being evaluated throughout the world. This will require:
   a. Implementation of a standard protocol at each project site.
   b. Training of local physicians at each site to carry out the protocol.
   c. Two members of the Dysmorphology Core traveling to each on a regular basis in order to verify the diagnosis made by local physicians and to update the training.
2. To explore the extent to which various degrees of deficient ($\leq 3^{rd}$ % vs. $\leq 10^{th}$%) anthropomorphic measurements, including length, weight, head circumference (OFC), palpebral fissures, inner canthal distance and philtrum should be used to enhance specificity of diagnosis without loss of sensitivity.
3. To explore strategies for diagnosis of FAS in the newborn period or at least during the first year of life.
4. To delineate the full range of structural anomalies in children prenatally exposed to alcohol and identify clinical features that are most indicative of future problems in neurobehavioral development in order to determine the boundaries that encompass Fetal Alcohol Spectrum Disorder (FASD).
5. To correlate the clinical diagnosis of FAS with that determined by 3-D photography.

B. & C. BACKGROUND AND SIGNIFICANCE AND PRELIMINARY STUDIES

The Fetal Alcohol Syndrome (FAS) initially described in 1973[1, 2] represents a spectrum of defects including variable degrees of growth deficiency, neurobehavioral deficits, and structural anomalies seen in the offspring of women who drink alcohol during their pregnancy. Although the brain is the developing structure most sensitive to alcohol, the diagnosis of FAS is presently

dependent not upon alterations in brain or behavior, but upon the identification of features noted on a careful physical examination including prenatal onset growth deficiency, microcephaly, and a characteristic pattern of minor malformations which is made up of subtle but distinct facial features, including short palpebral fissures, maxillary hypoplasia and a long smooth philtrum with a thin, smooth vermilion border of the upper lip, and

variable degrees of joint anomalies in addition to developmental delay or intellectual deficits. Since a behavioral phenotype specific for prenatal alcohol exposure has yet to be identified, it is not presently possible to diagnose FAS in the absence of this clinical phenotype. Unfortunately, this phenotype is frequently not recognized by other than the most experienced examiners. The result is underdiagnosis in some situations, usually occurring because the complete pattern of abnormalities cannot be substantiated often because of the patient's age, racial background or familial characteristics and overdiagnosis in others, usually because of too much emphasis on the maternal drinking history, the presence of non-specific abnormalities, or failure to recognize a different but similar multiple malformation syndrome.

Assurance that all children are appropriately diagnosed by a small number of physicians with expertise in diagnosis of FAS using a standard protocol is imperative relative to the integrity of each of the projects included in this Consortium. In addition, through ascertainment of a large number of children prenatally exposed to alcohol, members of the Dysmorphology Core will have the opportunity to develop more objective criteria for diagnosis of the full spectrum of alcohol related abnormalities.

Establishment of standard protocol for diagnosis of FAS in developing societies. (Specific Aim 1, 2 and 4).

An ongoing study of FAS in South Africa sponsored by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) began in I996 and is ongoing.[3] Three members of the Dysmorphology Core (KLJ, LKR, and HEH) represent three of the four designated expert dysmorphologists who carried out the clinical evaluation of all children in that study. The initial phase of the study used an active case ascertainment, 2-tier methodology among first-grade students from a rural community in the Western Cape Province of South Africa. Four, two-physician, teams (one expert dysmorphologist and one South African physician training in the diagnosis of FAS) worked independently but simultaneously. Of the 992 first-graders, 406 were examined by two different teams using a standard assessment of dysmorphic features and growth. A two-tiered screening system was used to evaluate the remaining 586 first graders. They were first assessed with respect to length, weight and head circumference (tier one). Children whose measurements were below the 10th percentile on head circumference or on both height and weight were referred for the complete examination (tier two) by the dysmorphology teams. Of these, 586 children, 222 met the growth criteria and were referred for complete examinations. Therefore, 628 children received full dysmorphology examinations. Based on the dysmorphology examinations, a child was assigned a preliminary diagnosis of FAS, deferred or not FAS. The deferred category included children with some facial features of FAS and growth deficiency but for whom further information was required for a final diagnosis; subsequent documentation of maternal alcohol exposure and results of neuropsychological evaluation were used to determine the final diagnosis (FAS or not FAS)

It is important to recognize that a significant educational component was built into this study. During the evaluation of the initial 406 children, a total of 12 South African physicians worked one-on-one for a two-day period with each of the expert dysmorphologists. During that time, each child was examined by both the South African physician and the dysmorphologist; palpebral fissure length, innercanthal distance, ear length and philtral lengths were measured and compared and the South African physician's final diagnosis was reviewed for accuracy. This exercise resulted in minimal interrater variability and demonstrated the fact that physicians with little or no expertise in diagnosing FAS can, through intensive training over a two-day period, be educated to do so.

A similar study, also sponsored by NIAAA is ongoing in Moscow, Russia.[4] Two members of Dysmorphology Core (KLJ and LKR) are the two designated expert dysmorphologists involved in that study. As opposed to using head circumference or height and weight below the 10th percentile in "normal" first-graders as an indication for complete physical examination, residents of Special Boarding Schools for mentally impaired children and Orphanages in Moscow were evaluated. Four Russian pediatricians were trained to diagnose FAS by Dr. Jones and Robinson. As of July 1, 2002, the four Russian pediatricians had evaluated 2,922 children at 30 facilities. During 3 one week visits to Moscow, the 384 children who the Russian

pediatricians diagnosed as having FAS or who they deferred for further evaluation were separately examined by the two dysmorphologists, who were blinded to the diagnosis of the Russian pediatrician and to the diagnosis of the other dysmorphologist. 143 of the 155 children diagnosed as FAS by the Russian pediatrician were confirmed to have FAS by both Dr. Jones and Dr. Robinson which provides good evidence of the ability to train physicians to accurately diagnose the extreme end of the spectrum of FASD in a relatively short period of time.

Diagnosis of FAS in newborn period (Specific Aims 3 and 5)

With the exception of only the most severe cases, recognition that a child has been affected by prenatal exposure to alcohol is extremely difficult in the newborn period, throughout the first year of life and even up to 4 years of age.

Stoler and Holmes[5] evaluated the frequency with which a group of general pediatricians on routine newborn examination recognized alcohol-related physical features in the offspring of a group of women recruited from a substance abuse clinic and a general obstetric clinic at a major inner-city teaching hospital. That the pediatricians were less effective than 2 highly experienced clinicians that were conducting a research study, which depended on performance of a careful time consuming physical examination, is not surprising. However, the extent of their under-recognition is surprising. One of 19 infants with prenatal alcohol exposure was noted by the general pediatricians to have alcohol-related physical features as opposed to seven infants, two of whom had FAS, identified by the two experienced study clinicians. The reason for this disparity is unknown, but most likely relates at least in part to the difficulty of documenting the characteristic physical feature of FAS in newborn infants. Accurate measurement of palpebral fissures requires that the infant lie still with eyes open. Crying causes contraction of the orbiculares oculi muscle and falsely shortens the palpebral fissure. Furthermore, mild degrees of ptosis are hard to detect, and the anatomy of the philtrum can be difficult to appreciate in an uncooperative, newborn infant. In addition, other characteristic facial features, such as low nasal bridge and short nose, are subjective, and epicanthal folds represent a variation of normal in many ethnic groups.

Given the relative lack of objective criteria and the need to rely on these clinical features, it is clear that recognition of this disorder requires a careful, time-consuming physical examination by an individual experienced in diagnosis of FAS who is aware that the child has been prenatally exposed to alcohol.

Early diagnosis of FASD is perhaps the most critical factor in providing appropriate resources for affected children that can provide optimum opportunities for their future development. Streissguth et al[6] showed the impact of secondary disabilities on individuals with FAS or Fetal Alcohol Effects and demonstrated that early diagnosis represented a "strong universal protective factor" which was associated with better outcome.

FAS-related craniofacial anomalies: relationship to defects in brain development. (Specific Aim 3)

In addition to the neurobehavioral deficits resulting from defects in brain development, a number of the unique craniofacial features characteristic of FAS are secondary to these brain anomalies, including short palpebral fissures and long smooth philtrum.

We have completed a pilot study in which we performed ultrasonographic studies of the eyes of 18 children with FAS as well as 104 normal individuals.[7] We concluded that palpebral fissure length is dependent on ocular size early in life, but that as we age other factors become more influential. Measurements on children with FAS indicated that the palpebral fissures in this disorder are associated with shorter ocular diameters. In that the optic vesicle is an out pouching of the frontal region of the brain, we concluded that the short palpebral fissure in FAS is reflective of abnormal brain development.

In a study of the normal and abnormal development and placement of the periocular structures the size and position of the bony orbit was documented to be determined by the position and size of the optic vesicle.[8] Thus, it is hypothesized that ultrasound documentation of a decreased diameter of the bony orbit may well be reflective of a small optic vesicle and thus short palpebral fissures.

Similarly, it has been suggested that the long smooth philtrum and thin vermilion of the upper lip are secondary to an alteration in forebrain development resulting in closely set olfactory placodes and underdeveloped medial nasal process. We evaluated development of the lateral philtral ridges (LPRs) in fetuses with FAS, holoprosencephaly, and bilateral cleft lip, three disorders with absent LPRs, and 20 normal human fetuses between 9 weeks and 20 weeks gestation. Based on gross histologic examination, we concluded that the LPRs develop as a result of a dynamic relationship between lip musculature, which derives from cells that migrate medially from the maxillary processes, and the frenulum of the upper lip. The latter is a midline structure, which derives from the medial nasal processes and as such is dependent on central nervous system development. Thus we hypothesized that the long smooth philtrum seen in children with FAS is indicative of an underlying defect in brain development related to the prenatal exposure to alcohol.[9]

We have furthermore shown that children with holoprosencephaly, a serious midline defect in brain development, which Sulik et al[10] noted in a mouse model of FAS, lack a superior labial frenulum.[11] Although children with FAS have a superior labial frenulum, its size and position have not been adequately evaluated. We have completed a pilot project evaluating the superior labial frenulum in normal children at various ages to develop a strategy for its measurement. We hypothesize that children with FAS have decreased size of the superior labial frenulum that can be determined clinically as early as the neonatal period.

Physical Features and Abnormal Growth Parameters Associated with Severity of Neurobehavioral Impairment (Specific Aim 2 and 4)

Dr. Miguel Del Campo's doctoral thesis that he successfully defended in 2002,[12] is entitled Correlation Between Physical Features and Cognitive Problems in Children Prenatally Exposed to Alcohol.

The main objective of his thesis was to determine whether the severity of the physical phenotype is associated with the severity of the cognitive impairment. Specifically, he searched to determine which of the dysmorphic features and altered growth parameters were associated or correlated with the severity of the cognitive impairment in order to stratify the importance of minor anomalies and altered growth parameters in predicting cognitive impairment after prenatal alcohol exposure. Sixty-one patients were included in the study. All attended the Dysmorphology Clinic at UCSD Medical Center during the 4-year period of l995-1999. For all patients high maternal alcohol intake in pregnancy was documented. All children were subjected to a complete physical exam with specific physical measurements and a detailed search for minor anomalies, and a battery of multiple neuropsychological tests were used to evaluate the cognitive impairment. The following quantitative variables demonstrated a statistically significant correlation with the outcome variables FSIQ, VIQ and PIQ: Age at diagnosis, age at testing, height, OFC, scores for smooth philtrum and smooth vermilion border of the upper lip, and number of physical diagnostic criteria of FAS. The following qualitative variables demonstrated a statistically significant association with the outcome variables: FSIQ, VIQ and PIQ: Gender, ptosis, smooth philtrum, abnormal palmar creases, hockey-stick crease and number of diagnostic criteria. OFC and hockey stick crease were the only statistically significant variables in the multiple linear regression analysis. Several multiple regression trees established a stratification of the quantitative and qualitative variables in their ability to divide the sample according to differences in IQ. The following conclusions were made:

1. Following prenatal exposure to alcohol, certain physical features are significantly associated or correlated with cognitive development in a population of 61 patients with prenatal exposure to alcohol. These are OFC, height, ptosis, a smooth philtrum and upper lip, the hockey stick crease and other abnormal palmar creases.
2. Among these, those that show a greater independent association and correlation with cognitive impairment are decreased head circumference and the hockey stick crease.

3. The physical features can be stratified according to their ability to predict cognitive deficit as follows:
   a) Major diagnostic criteria with prognostic value: decreased OFC and the hockey stick crease.
   b) Minor diagnostic criteria with prognostic value: postnatal growth retardation, smooth philtrum and thin vermilion border of the upper lip, ptosis and abnormal palmar creases (other than the hockey stick crease).
   c) Diagnostic criteria with no prognostic value: birth weight, palpebral fissure length, philtrum length, camptodactyly and limitation of elbow pronation-supination. We were surprised at the lack of correlation between palpebral fissure lengths and cognitive function and can only speculate that it is a function of lack of variation of palpebral fissure length.

Integration with and contribution to goals of the consortium:

The Dysmorphology Core will be contributing to the goals of the Consortium by supporting all studies with human subjects. Members of the Core will be responsible for assuring accuracy of diagnosis of FAS in all consortium sites and as such will document the full range of effects from prenatal exposure to large and moderate amounts of alcohol. This will be accomplished by implementing a standard protocol for diagnosis that will be used in all study sites. This will allow for better definition of the effects from prenatal alcohol exposure and will aid in developing more accurate ways of ascertaining these effects, which can be implemented on a broad scale.

Administration and Management of the Core:

The professional staff of the Dysmorphology Core includes Dr. Kenneth Lyons Jones (Director), Dr. Luther Robinson, Dr. H. Eugene Hoyme and Dr. Miguel Del Campo. The latter 3 individuals were all Fellows in Dysmorphology with Dr. Jones at the University of California, San Diego.

Dr. Jones will assume overall responsibility for budget issues relative to the Core and he will be responsible for organizing travel and all activities regarding physical examinations at the different consortium sites as well as analysis of the data. He will assume day-to-day responsibility for the Administrative Assistant and will be responsible for maintaining the records of the dysmorphology examinations performed at the different sites. The Core PI and the Consortium Director will meet on a quarterly basis to review scientific progress and to ensure the availability of Core services to each of the Consortium sites. Dr. Jones' office at UCSD Medical Center is approximately 10 miles distance from Dr. Riley's office at the Center for Behavioral Teratology at San Diego State University.

Services for New Projects Added to Consortium:

New Pilot Projects that are added to the consortium for which documentation of the clinical phenotype is necessary will be provided the same services by the Dysmorphology Core as the initially funded projects. As in the case with the pilot projects funded in Year 01, funding will be assumed by the Pilot Project.

D. RESEARCH DESIGN and METHODS

We intend to support human studies internationally in South Africa, Russia, Finland, Italy, and the Ukraine. In the United States we will support projects in Seattle, Washington, Atlanta, Georgia, San Diego, California, and Buffalo, New York. This will assure correct and consistent diagnosis of FAS. Documentation of growth parameters as well as major and minor malformations in large numbers of children, at various ages, with FAS will provide more objectivity in diagnosis at various ages. In addition, the data resulting from these studies will provide the opportunity to document the full range of structural anomalies in FAS and determine features on the physical examination that are predictive of altered neurobehavioral development.

I. ***Consortium Sites and Projects for which Dysmorpholgy Core will provide support:***

1. *Prospective Study in Moscow Region of Russia.* The purpose of this project is to measure in a prospective sample, the full range of FAS in children born to women who are moderate to heavy drinkers, to compare these results with the range of FAS as characterized in retrospective samples and to test the possible protective effects of nutritional intervention in a group of moderate to heavy alcohol-using women. In this study, it will be possible to document the phenotypic features in prenatally exposed neonates who do not meet the criteria for FAS in order to determine the full range of the FAS phenotype.

   The Dysmorphology Core will be responsible for clinical recognition of FAS based on physical examination performed on all liveborn children in the study at birth and again at 18 months of age. This will involve examinations of approximately 1200 children at the designated times over the 5 years of the study. Although 4 local pediatricians have previously been trained to diagnose children with FAS, the majority of these children have been between 6 and 14 years of age. None have been newborns or 18 months of age. Therefore, the four local pediatricians will require additional training in diagnosis of FASD at those younger ages by members of the Core.

2. *Neurobehavioral Development of Children with FASD.*
   Dr. Robinson and Dr. Jones have previously identified large numbers of children with FAS in Special Boarding Schools and Orphanages in Moscow. They have also trained 4 pediatricians in Russia to diagnose FAS. This study represents an extension of that study. Its purpose is to document neurobehavioral abnormalities that are specific for prenatal alcohol exposure i.e. identification of a behavioral phenotype. As such it is imperative that each child assumed to have FASD by the neuropsychologist has been appropriately evaluated from the standpoint of their clinical phenotype. The Dysmorphology CORE will be responsible for providing that assurance. Approximately 200 additional children each year will be evaluated. This represents the number of new admissions to the Boarding Schools and Orphanages in Moscow each year.

3. *Prenatal Ultrasound Markers of FASD in Ukraine:* This project will evaluate early markers of prenatal alcohol exposure. Standard 2-D prenatal ultrasounds will be performed at 4 specific time periods on 80 moderate-to-heavy-drinking pregnant women and a similar number of minimal to non-drinking controls. The investigators will determine the extent to which prenatal alcohol impacts somatic as well as brain growth. In addition, existing 3-D ultrasound equipment will be used to explore the capability of identifying abnormalities of brain and facial development in fetuses exposed to heavy alcohol. Clinical evaluation in the neonatal period will be the responsibility of the Dysmorphology Core.

4. *FASD Epidemiology in Italy*: This is a prior study of the epidemiology of FASD in the Lazio region of Italy. In two consecutive years a random sample of 25 schools in the region will be picked and all first grade children in these schools assessed for FAS using the two tier procedure outlined in the Dysmorphology Core. One hundred randomly selected controls will

also be examined each year. All controls and those with some dysmorphological characteristics of FASD will be advanced to psychological testing. Extensive maternal risk factor interviews will be administered to all mothers to establish protective and risk factors for FASD. The results of this study will provide a valid estimate of the true prevalence of FASD in this region of Italy. Furthermore, it will identify specific maternal risk and protective factors, specific characteristics of the FASD and normal children in this region, and insights into possible and feasible approaches to prevention and intervention where needed.

5. *Detecting FASD from Neonatal Ultrasound*: The Seattle group has recently shown in a series of 3 papers, that adults and adolescents with FAS or FAE can be detected with over 80% accuracy from controls with a method developed by Bookstein for measuring shape variability of the corpus callosum (CC) from MRI. Furthermore, both diagnostic groups were equally deviant in CC shape, which in turn detected 2 profiles of neuropsychological deficit: motor and executive function (EF). To extrapolate this work to newborn babies, the Seattle group has now carried out a successful feasibility study developing a method of averaging ultrasound images of the CC which revealed a hypoplastic CC in 3 of the 4 alcohol exposed and none of the controls. In this pilot investigation they expect to demonstrate significant differences in shape variation of the CC between 25 heavier alcohol exposed babies and 25 unexposed. Evaluation of these 50 neonates will be the responsibility of the Dysmorphology Core.

6. *Comparison of Three Diagnostic Modalities in FASD and Related Disorders in African Americans*: Epidemiological studies in the US suggest that FASD is more common among African Americans than persons of European background. A critical question, however, concerns whether facial features that are associated with FASD (e.g., depressed nasal bridge, and epicanthal folds) also are common normal variations among Africa Americans and may contribute to over diagnosis of FASD in this group. In Buffalo, there is the opportunity to study this question by articulating the clinical efforts with the Consortium to assess the facial morphology of FAS and related disorders among African American subjects in comparison with similar subjects of European background. Individuals with Williams syndrome, an autosomal dominantly inherited disorder with craniofacial dysmorphism will serve as a disease control. Subjects will be recruited from the Ambulatory and Genetics Division in the Department of Pediatrics at SUNY-Buffalo. We will collaborate with researchers at Indiana University to compare and correlate three assessment modalities –dysmorphology, selected anthropometric measures and three dimensional (3-D) digital imaging –to generate and analyze data (e.g., regression analysis, discriminate function analysis) that allow more reliable recognition of FASD in this population. The Dysmorphology Core will be responsible for the clinical evaluation of all subjects and controls in the pilot project.

7. *Neurobehavioral Studies in Atlanta, Georgia:* 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 be imaged and particular attention 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 Dysmorphology Core will be responsible for clinical evaluation of each of these children.

8. *Neurobehavioral Studies in South Africa and the United States:* Dr. May will oversee a project that will take place in both South African 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 African and over 100 cases through the University of New Mexico. The Dysmorphology Core will be responsible for Clinical Evaluation of each of these children.

9. *Neuroimaging Studies in Finland*: FASD research has been ongoing in Finland for over 15 years. Four separate studies will be conducted on adolescents and young adults that have earlier been assigned diagnoses of FASD. Validation of these diagnoses will be the responsibility of the Dysmorphology Core.

II. *Maternal Alcohol Interview*

1. *For Prospective Maternal Alcohol Interviewing*

An in-depth, quantitative interview using a timeline follow-back procedure[13,14] will be administered to each mother regarding her use of alcohol, smoking, and illicit drugs during pregnancy. In the perspective studies, during the first interview administered during pregnancy, the mother will be asked about her drinking during a typical week at the time of conception, with recall linked to specific times of day and activities. She will then be asked whether her drinking has changed since that time and, if so, when it changed and how much she now drinks on a day-by-day basis during a typical week. The mother will be interviewed again shortly after delivery and asked whether her drinking changed during the latter part of pregnancy after she was interviewed and, if so, when it changed and how much she then drank on a day-by-day basis during a typical week. Volume will be recorded during each interview for each type of beverage consumed each day, converted to oz absolute alcohol (AA) per day using multipliers proposed by Bowman et al.[15] (0.4 for liquor, 0.04 for beer, 0.2 for wine), and summed to provide a measure of average oz AA consumed during pregnancy. Average AA per drinking day (dose per occasion) and proportion of drinking days (frequency of drinking) will also be calculated. These three summary measures can also be constructed for the period around the time of conception and for each trimester of pregnancy. Mothers will also be interviewed regarding frequency of binge drinking (5 or more drinks/occasion) during each trimester of pregnancy. At a postnatal visit (6-12 months postpartum), mothers will be interviewed regarding their alcohol use during a typical week following delivery.

Each mother will also be administered the alcohol abuse and dependence module from the Diagnostic Interview Schedule, Version IV[16] to determine whether she meets DSM-IV diagnostic criteria for alcohol abuse or dependence. In addition, she will be asked at what age she started drinking on a regular basis and will be administered the TWEAK[17], a 5-item screening instrument which includes an excellent tolerance question (How much alcohol can you hold?) that detects problem drinkers without directly asking them about how much they have been drinking.

In each of these interviews conducted during pregnancy and following delivery, the mother will also be asked how many cigarettes she smokes each day on average, which illicit drugs she uses, and how frequently she uses each, and at what age she started using these on a regular basis. Because of the wide variability in the dosage and degree of purity of commonly used substances, exposure will be summarized in terms of the average number of days per month each of five categories of drugs are used: marijuana, cocaine, other stimulants, opiates (e.g., heroin, methadone, codeine), or depressants.

This maternal alcohol interview has been used and validated in a large prospective, longitudinal study of inner-city African-American women in Detroit, Michigan,[18,19,14,20,21,22,23] cross-culturally in

a study of heavy alcohol using women in Cape Town, South Africa[24,25,26,27] and in a study of Inuit women in northern Quebec.[28] When necessary, culturally appropriate, study specific modifications may be incorporated with the advice of the Core.

2. *For Retrospective Maternal Alcohol Interviewing*
The same questions will be asked in those studies for which the methodology calls for retrospective ascertainment of children prenatally exposed to alcohol. For those studies, the questions will be asked on one occasion. As is the case for the prospective maternal alcohol interviews, culturally appropriate, study specific modifications may be incorporated with advice from the Core.

III. *Standard Protocol for Evaluation of children for Diagnosis of FAS.*

1. *Two-Tier Methodology:*
All liveborn infants (Moscow Region, Ukraine, and Seattle, WA) or older children (Finland, Moscow, Rome, South Africa, Atlanta, GA and San Diego, CA) will receive a standard assessment of dysmorphic features and growth (See Appendix 1). A 2-tier methodology will be used at all sites. Each child will first be assessed using a standardized protocol by a local pediatrician who has been trained by members of the Dysmorphology Core (Tier 1). Based on the initial assessment, a child will be assigned a preliminary diagnosis of FAS, Deferred, or not FAS (see criteria for FAS classification, below).

Children with a diagnosis of FAS or Deferred by the local pediatrician will be referred for a standardized physical examination by two expert dysmorphologists (Tier 2). Each child will be examined by each of the expert dysmorphologists who is blinded to the diagnosis of the other and to the diagnosis of the local pediatricians. Based on that examination the child will be assigned a diagnosis of FAS, not FAS or Deferred. Children categorized by the expert dysmorphologists, as Deferred will require completion of the physical exam at the end of the study as well as the neurobehavioral evaluation in order to come up with a final diagnosis. If there is evidence of neurobehavioral deficits but without microcephaly, the child has 2 or more facial features characteristics of FAS, and is growth deficient, the child will be designated FAS. Otherwise, the child will be designated, Some Alcohol-Related Features. This category will make up the cohort of which the full range of FASD can be determined.

2. *Criteria for FAS Classification:*
The following criteria for classification are based on Institute of Medicine guidelines as well as the diagnostic algorithm developed for studies previously and currently being conducted in South Africa and in Russia. The use of comparable diagnostic criteria will enhance comparisons with other study results.
a) FAS: subjects who have the constellation of the following features will be classified in this group.
    i. Growth deficiency defined as prenatal or postnatal weight and/or height ≤ 10th % for sex and age using National Center for Health Statistics current growth charts (and adjusted for prematurity for growth measurements at the first evaluation for infants less than 12 months of age).
    ii. At least two of the following facial features:
        •palpebral fissure length unilaterally or bilaterally ≤10th % for age (and adjusted for prematurity for measurements at the first evaluation for infants less than 12 months of age)
        •philtrum smoothness using the Astley/Clarren Lipometer[29] valued at 4 or 5
        •thin smooth vermilion border of the upper lip using the Astley/Clarren Lipometer valued at 4 or 5.

•Maxillary hypoplasia

iii. Neurobehavioral/Neurodevelopment: Microcephaly defined as OFC ≤10th centile adjusted for age and gender; obvious structural brain abnormalities and/or confirmed neurodevelopmental or neurobehavioral disorder in areas of: attention, memory, motor function, language, cognitive, and socio-economical development, with or without mental retardation.

b) Deferred Classification for FAS. This category will be broader for the local pediatricians than for the dysmorphologists in order to provide the opportunity for more children to receive a validating examination by the dysmorphologist. For the local pediatrician, subjects will be deferred who have growth deficiency defined as weight OR height equal to ≤ 10th centile for age using the National Center for Health Statistics current growth charts (and adjusted for prematurity for growth measurements for infants less than 12 months of age), and who have either of the following two criteria:

i. at least one facial feature as defined in FAS criteria above or
ii. any additional feature listed on the Examination Form set forth by the Dysmorphology Core such as ptosis, rail road track ears, hockey stick palmar crease, other palmar crease abnormalities, joint contractures, decreased pronation/supination at the elbows, hirsuitism, a heart murmur determined to be indicative of a cardiac defect.

For the expert dysmorphologist, the deferred category, as stated above in C-1 (Two-Tier Methodology) will be used for children who require completion of the physical exam at the end of the study as well as the neurobehavioral evaluation in order to arrive at a final diagnosis.

c) Some Alcohol – Related Features: Subjects who have any one of

i. one or more facial features as defined in FAS Criteria above
ii. additional features listed on the Examination Form set forth by the Dysmorphology Core such as ptosis, rail road track ears, hockey stick palmar crease, other palmar crease abnormalities, maxillary hypoplasia, decreased pronation/supination at the elbow, hirsuitism, a heart murmur determined to be indicative of a cardiac defect. These are listed in the Appendix I for the Dysmorphology Core.
iii. Growth deficiency defined as height OR weight, ≤ 10th centile.
iv. OFC ≤ 10th centile.

Subjects with these features but who do not meet the criteria for FAS will be placed in this category. Therefore deferred children who do not subsequently become classified as FAS will ultimately be included in this group. This classification, although not FAS, is analogous to the Alcohol Related Birth Defects ARBD classification as outlined in the Institute of Medicine Report and will make up the cohort of which the full range of the FASD can be determined.

d) Explanation for Use of Two-Tiered Methodology.

The two-tiered methodology for evaluation of children for diagnosis of FAS that is proposed for the Dysmorphology Core has been tested in two international sites (Moscow, Russia and South Africa) and has been determined to be an effective means of diagnosing FAS. Although not used internationally, a 4-digit system for diagnosis of FAS has been developed by Astley and Clarren and has been used in a number of sites throughout the United States and Canada. That system has not been validated and our plan is to attempt to do so in the study conducted in the Moscow Region of Russia. Furthermore certain aspects of that system will be used including the Astley/Clarren Lipometer for categorization of philtral smoothness as well as

thinness and smoothness of the vermilion border. In addition to the lack of validation of the system developed by Astley and Clarren, the diagnostic categories that have been developed result in the misclassification of many children who have FAS as other diagnoses. In that validation of this system by investigators other than the developers of the system has not occurred and because agreement regarding the constellation of features that allows diagnosis of FAS has not been arrived at, it is felt that the Astley/Clarren system for diagnosis is not appropriate for use in the Consortium as the primary method for diagnosis of FAS.

3. *Evaluation of Additional Features.*

a) All children identified in the neonatal period (Moscow Region, Seattle, WA) will be evaluated for their nutritional status using a Clinical Assessment of Nutritional Status Score (CANSCORE). A single page form (see Appendix 2) will be used to rate nine superficial, easily detectable signs of malnutrition in the neonatal period. These include:

i. Hair silky vs. straight
ii. Buccal fat in the cheeks.
iii. Sharply defined thin or fat double chins, which usually obscure the neck in well-nourished neonates.
iv. A thin clearly evident neck with loose wrinkled skin.
v. "Accordion" pleating of the skin of arms with loose, easily lifted skin over elbows.
vi. "Accordion" pleating of the skin of the legs with loose, easily lifted skin over knees and anterior femur.
vii. Sunken intercostal spaces on the chest, and loss of subcutaneous fat on back with loose skin easily lifted.
viii. Minimal fat and wrinkled skin on abdomen.
ix. Buttocks with deep folds.

Each of these signs will be rated 1 (worst, severe fetal malnutrition) to 4 (best, well nourished). Thus the CANSCORE ratings vary from 36 (highest) to 9 (lowest).

b) A representative sample of neonates born to high and moderate drinking mothers in Ukraine in addition to non-drinking mothers as well as a representative sample of 8-10 year old children with FASD identified in Boarding Schools and Orphanages in Moscow in addition to 8-10 year old control children will be evaluated relative to the size of the superior labial frenulum to determine if it is decreased in children with FASD and if so, if it varies based on severity of the neurobehavioral deficit.

4. *Training of Local Physicians*

Depending on the numbers of children who will be evaluated, at least 2 local pediatricians will be identified at each consortium site. Prior to doing any clinical assessments on his/her own, each of the local pediatricians will work one-on-one for a two day period with at least one of the 4 expert dysmorphologists. During that time, each child will be examined by both the local pediatricians and the dysmorphologist; palpebral fissure length, inner canthal distance, head circumference and philtral lengths will be measured and compared and the local physicians final diagnosis will be reviewed for accuracy. Only in those situations in which the local pediatrician is able to demonstrate his/her ability to consistently measure the palpebral fissure within 1 mm and the inner canthal distance and philtrum within 2 mm of the expert dysmorphologist will that individual be approved for the study.

5. *Interpretation of Data*

As the data resulting from these exams is obtained (**Specific Aim 1**) and is combined with the neurobehavioral data from the Neurobehavioral Core we will, through interaction with the Informatic Core, be able to use these data sets to begin to answer Specific Aims 2-6.

Specific Aim 2 – To explore the extent to which various degrees of growth deficiency (3rd % vs. ≤10th %), anthropomorphic measurements including length, weight, head circumference (OFC), palpebral fissures, innercanthal distance and philtrum, should be used to enhance specificity of diagnosis without loss of sensitivity.

Dr. Jones (Co-Chairman) and Dr. Robinson have both been on a CDC/NCBDDD Scientific Working Group for Diagnostic Guidelines for FAS and ARND. Although specific growth criteria have been established for diagnosis of FAS by the working group, there remains significant controversy as to whether the cut off for palpebral fissure length, as well as length, weight and head circumference should be the 10th % or the 3rd %. Since these measurements are objective features of FAS, this issue has significant importance, particularly from the standpoint of developing community based screening criteria for FAS. Growth data from children who have been diagnosed as having FAS and from those diagnosed as not FAS by the Dysmorphology Core at all Consortium sites will be utilized to determine the extent to which ≤ 10th % as opposed to ≤ 3rd % for palpebral fissure length would result in misclassification of large numbers of children who do not have FAS. Similar comparisons will be done with length, weight and head circumference. This analysis will be performed in order to set guidelines that will enhance specificity while at the same time maintaining sensitivity of the diagnosis and also to set the boundaries that encompass FASD.

Specific Aim 3 – To explore strategies for diagnosis of FAS in the newborn period or at least during the first year of life.

Data from physical examinations at birth and at 18 months of age will be available from the Prospective Study in the Moscow Region and at birth from the two pilot projects one in Ukraine and one in Seattle WA. Children identified on physical examination to have FAS will provide the opportunity to evaluate manifestations identifiable through prenatal ultrasound such as growth deficiency in Moscow and, deficiency of the frontal area of the brain, as well as growth deficiency in Ukraine. Postnatal ultrasound evaluations in the neonatal period will permit evaluation of the corpus callosum. Evaluation of the size of the superior labial frenulum will provide the opportunity to explore the possibility of identifying another objective feature of FAS and newborn photographs using a standardized methodology developed in older children by Astley and Clarren[13] will be utilized in the newborn period and at 18 months to determine its applicability at younger ages. Finally correlation of the clinical diagnosis of FAS with that determined by 3-D photography obtained from the 3D Imaging Core can be determined in the newborn period as well as in older children.

Specific Aim 4 – To delineate the full range of structural anomalies in children with FASD and identify clinical features that are most indicative of future problems in neurobehavioral development.

With respect to the former, based on the accumulated physical examinations, it will be possible to document the complete spectrum of defects seen in children with FASD at various ages. This will be particularly relevant in the prospective studies in Moscow, Seattle WA and Ukraine in that these children will be ascertained in the neonatal period by virtue of their mother's consumption of alcohol during pregnancy as opposed to being ascertained based on structural defects characteristic of FAS. Furthermore, the Some Alcohol-Related Features Category will provide the opportunity to determine the relevance of features on the Dysmorphology Core Physical Examination that are seen more frequently with FAS in children who do not meet the established criteria for FAS. This category will be most important in establishing the full range of FASD.

In order to explore the issue of identifying clinical features that are most indicative of future problems in neurobehavioral development, we will analyze the data from the prospective studies in which neurobehavioral outcome is documented (Moscow, Seattle WA, South Africa, Ukraine,

Atlanta GA, Native Americans)) in the same fashion as was done in Dr. Del Campo's Ph.D. thesis (see Background and Significance) entitled Correlation Between Physical Features and Cognitive Problems in Children Prenatally Exposed to Alcohol. We will determine which variables or features (alterations of growth, minor and major malformations) seen in babies prenatally exposed to alcohol contribute to the greatest variation in IQ. After ascertaining all prenatally exposed infants and collating all variables, statistical univariate and multivariate analysis will be used to determine the correlation of these variables with variation in IQ using appropriate tests according to the characteristics of the variable: the t test, the Mann-Whitney U test, the Kruskall-Walles test, a generalized linear regression model and regression trees. Additionally, the Informatic Core will provide assistance in the appropriate statistical tests and with statistical modeling. Appropriate analysis depends on having an accurate and consistent physical exam across all consortium sites. It will be important to determine if by using the same approach in a prospective sample of neonates, the same features or combination of features or others as were noted in the retrospective study will be predictive of IQ.

Specific Aim 5 – To correlate the clinical diagnosis of FASD with that determined by 3-D photograph.

Growth and physical features of children of all ages at all consortium sites will be used to correlate physical features of FASD including growth measurements with features documented on 3-D photography.

E. HUMAN SUBJECTS

Gender and minority inclusion for research involving human subjects

Women will be the only adult subjects enrolled in this study because the area of research involves pregnancy. Both male and female children will be involved in the postnatal clinical evaluations. No ethnic group will be excluded. However, based on the racial/ethnic composition of the consortium sites, the subjects recruited will be White, African Americans, Native Americans, and Cape-Colored.

Participation of children

Children, i.e., females under the age of 21 who are pregnant and who meet the alcohol consumption criteria will not be excluded from this study. Children will be the focus of the postnatal clinical evaluations with the consent of the parent.

Human Subjects

• The human subjects participating in the Dysmorphology Core will be the liveborn children of pregnant women receiving care at participating birthing hospital sites in the Moscow Region of Russia, Ukraine and Seattle, Washington, and children ascertained retrospectively in consortium sites in Rome, Italy, Finland, San Diego, California, Atlanta, Georgia, South Africa and in the Native American population of the Great Plains. Approximately 4000 children will be evaluated over the five years of the project. The children will range in age from birth through 10 years of age. There will be a small number of adults with FASD.

• Research material will be collected from individually identifiable living human subjects; however, data in the final format for analysis will be stripped of personal identifiers. The data from the clinical evaluations as well as ultrasounds will be obtained specifically for research purposes. Physical assessments could be important to the health of the children involved in the studies and so they will be made available to the subject's parents if they so desire.

• The mothers of subjects in the Moscow Region, Seattle Washington, and Ukraine sites will be recruited from existing hospital sites from among pregnant women who are already receiving care at these locations. The study interviewer will consent the mother of each subject at the time she is enrolled at the site. The interviewer will explain the study objectives, requirements, benefit and risks, and will obtain written consent if the subject's mother agrees to participate. A copy of the signed consents will be maintained at the Coordinating Center in San Diego, California at the UCSD Medical Center in the office of Dr. Jones.

• There may be some discomfort associated with the physical exam but no more than would be normally encountered during a routine pediatric examination.

• The study personnel will be responsible for maintaining restricted access to subject data through use of locked files, computer passwords and precautions when transmitting data.

• The anticipated potential risks to the subject in this protocol are far outweighed by the benefits to this subject and to society. For the subject, the benefits are specialized evaluation with respect to the

effects of prenatal alcohol exposure and appropriate referral if the child is effected. Benefits to the public health of the community at large can result from the research goals of this study being realized. Among other benefits, knowledge regarding the prevalence of FASD among the offspring of alcohol/exposed women will provide valuable information regarding the range and prevalence of abnormalities associated with FASD, risk factors including those that are modifiable for FASD, and projected numbers of children in the various consortium sites requiring future service related to this disorder.

Targeted/Planned Enrollment Table
This report format should NOT be used for data collection from study participants.

Study Title: Dysmrophology Core

Total Planned Enrollment: 4,000

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino			
Not Hispanic or Latino	2,000	2,000	4,000
Ethnic Category Total of All Subjects*	2,000	2,000	4,000
Racial Categories			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American	75	75	150
White	1,925	1,925	3850
Racial Categories: Total of All Subjects *	2,000	2,000	4,000

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."

F. Vertebrate Animals

None Used

G. Literature Cited

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