ADMINISTRATIVE CORE CONFERENCE CALL

Date/Time	April 29, 2004 @ 12:32 pm
Attendees	Ed Riley, Michael Charness, Tatiana Foroud, Kenneth Lyons Jones, Sarah Mattson, Deidre Roach, Jennifer Thomas and Maudray Hogan.

ISSUE	RECOMMENDATION/DISCUSSION
Administrative/Manuals	There is a strong concern that South African is already testing without the manuals. PIs did not want to wait because they had trips and subjects already scheduled. Dr. Mattson stressed concern regarding this issue – she wanted investigators to wait until the manuals were complete so that everyone would be doing the testing in the same way. This issue could have been diverted had they waited. Dr. Mattson requested feedback from Neurobehavior Core regarding reliability procedures to record testing at different sites, but so far has not had any feedback, except for finished collaborators who weren't happy with the procedure. Need more control regarding consistency in using the manuals; everyone agreed to this while in San Diego. Finland has had concerns on issue of data sharing however; we think we have reassured them. Steering Committee needs to strongly endorse use of manuals. Reliability Issue – disadvantage is cost. We need to bear the cost to make sure that everyone is using the same protocols and procedures. Joe Jacobson has drawn up authorship and publication documents Concern with Informatics Core – they want right of authorship. This issue needs to be addressed. All subcontracts have been signed. A reasonable number of abstracts have been submitted to RSA, Teratology, etc.
Dysmorphology Core	Dr. Jones went over procedure used regarding control groups. Need consistency with control groups as much as possible across sites. Dr. Riley felt that the controls were more inclusive and that we could eliminate subjects to make the groups more uniform. Physical exam and diagnosis will remain the same. Dr. Riley's concern – Are the alcohol exposed kids in the control groups? We will discuss this matter further in June, 2004. Concern was raised about the Seattle pilot project not utilizing the dysmorphology core. It was stressed that Seattle is the only site doing this type of work and that the dysmorphology exams could be done post hoc in this case. However, they are not using forms that Christina Chambers and Sandy Jacobson have designed for maternal alcohol measures. Seattle is planning a R01 based upon this pilot and the question arose if this will be converted to a U01.
Informatics Core	Andy Arenson as well as others have been promoted and will be replaced. Ed will speak with Craig Stewart regarding this issue and the slow progress in the informatics Core.
Administrative Core	Joe Jacobson has drawn up authorship and publication documents Concern with Informatics Core – they want right of authorship. This issue needs to be addressed. All subcontracts have been signed.

	A reasonable number of abstracts have been submitted to RSA, Teratology, etc.
New Business/ Comments	Web designer is having problems with firewalls. Implementing a protected site only available to PI's. All agreed that forms should be standardized. It is critical before Vancouver that Deidre Roach or Ken Warren send out a letter stressing that under no circumstances can anyone go off on their own without following manual procedures. If they don't choose to cooperate, Ed will argue strongly that their funding would be limited until they come around. We would be open to modifications.
Meeting Adjourned	1:20 pm.

Submitted progress reports are attached.

Agenda Items/Project Updates as of 04/26/04

CORES:

Ed Riley - Administrative Core:

- Work continues on the website: http://www.sci.sdsu.edu/CIFASD/index.htm
- Awaiting forms and manuals to be loaded to website (dysmorphology form and manual, neurobehavioral manual, maternal questionnaires.
- All contracts are in place
- We are beginning to put together information for certificate of confidentiality.
- Putting together names for Science Advisory Panel.
- Dealing with problems from individual projects.
- Draft of authorship and publication statement is under revision after obtaining comments from the PIs

Ed Riley - Pilot Project Core:

- **Phil May – International Neuropsychological Study of FASD:**
  Currently in Italy with the epidemiolgy team where we will be finished doing the dysmorphology and maternal interviews of all of the first wave children for the Italy pilot project. Thus, by the end of the week we will be about 60% done with the data collection for the first wave of our two year (two wave) study. All is going well.
- **Ann P. Streissguth – Pilot Project 3-Detecting FASD from Neonatal Ultrasound:**
  As of April 23, we have completed recruitment and ultrasound exams on 20 patients. We have had three presentations on the project accepted for the Teratology Meetings in Vancouver B.C., June 2004:
  A. Platform talk:
    - Bookstein, Streissguth, Cleason, Lalani, Connor, Keener, Baldwin and Green: Ultrasound imaging of the Neonatal Corpus Callosum is Feasible and Useful.

  B. Posters:
    - Whitney, Streissguth, Bookstein, and Grant: Neonatal Cranial Ultrasound Leads to Early Diagnosis and Early Intervention in Baby of Alcohol-Abusing Mother: A Case Report.
    - Huggins, Grant, Ernst, Barr and Streissguth: Screening for FASD at Delivery.
    - We are writing an R01 on an expanded baby ultrasound grant: "Detection of FASD by Neonatal Intracranial Ultrasound."
    - The neonatal ultrasound project is now underway at the principal birthing hospital in Vienna, under the direction of Arnold Pollack, director of Neonatology. Fred Bookstein is the chief scientist for the project. A description of the study is posted on the federal ministry web site, as is the press release from earlier in April announcing the Austrian vision of the public health significance of the work.

Andy Arenson - Informatics Core:

I hate to admit it, but we have done a very poor job in the last four weeks of responding in a timely fashion.

- Dysmorphology—Informatics owes new version of Access DB to Ludmilla
- 3D Facial Imaging—ok
- Brain Imaging—Informatics owes Elizabeth comments
- Neurobehavior Child—Informatics owes Sarah comments
- Neurobehavior Infant—no action to date
- Ultrasound prenatal—Informatics owes Tina comments
- Ultrasound postnatal—no action to date
- Maternal data—Waiting on new form from Sandy/Tina
- Cofactors—Informatics owes Sandy comments
- LAB data—no action to date
- Intervention Child—no action to date

- Intervention Mother—no action to date

There are a variety of contributing factors to this, but regardless, we are clearly underperforming at this point. When I get my replacement hired, which I expect to be in about four to six weeks from now, they will begin working nearly full time on this project to make up the lack of effort in recent weeks. In the meantime, Joe and I are attempting to make sure that they most critical items
are handled.

CLINICAL CORES
Neurobehavioral Cluster
Ed Riley - Neurobehavioral Core:

- All available tests have been sent to each of the testing sites.
- We are still awaiting two tests
- Concerns over individual sites altering the proposed battery have been dealt with.
- Concern over the Leiter-R as a measure of IQ

Have spoken with the author of the revised test and am collating his response to send to the field.
Have spoken with two individuals who have used the Leiter-R with children with full verbal abilities and they have provided some insight into why one site may have had problems.
We are making a video of the testing procedure.

Elizabeth Sowell – Brain Imaging:

As of this time, we have made progress in numerous aspects of the proposed function of the Imaging Core for the CIFASD since our last progress report in March of 2004.

A. Mechanical Phantom: The Movie
We have purchased the mechanical phantom proposed for calibration of the brain imaging data from various image collection sites. We have developed a protocol for filling the plexiglass phantom, and perfected the recipe. We are in the process of producing a digital video of the procedure for filling the phantom with distilled water, saline, antibacterial soap, and gadolinium contrast agent. While it may seem simple, it was quite a complicated process to determine the most efficient and effective way of filling the container (phantom) the container while reducing the number of air bubbles that inevitably appear as the plexiglass container is filled with water. This is critical as the phantom cannot be shipped with the contrast agent inside, and thus the phantom will have to be refilled at each research site. The digital video will illustrate each step in the process, and help educate Consortium members faced with the task. We will produce a CD with the phantom "movie," which we plan to ship to Ed Riley along with the phantom before his trip to Moscow. We have determined that the contrast agent (liquid gadolinium) which must be extracted from its container with a needle and syringe, and saline solution (white powder substance) should be shipped to each site via Fed Ex (if they go to Moscow?) as these items may not be legally carried on an airplane. Distilled water would be the only ingredient that would have to be obtained at the specific research sites.

B. Mechanical Phantom: Scanning
We have scanned the mechanical phantom in our 1.5 Tesla research dedicated magnet where we will be studying FASD participants. We have begun to conduct experiments designed to assess the effects of refilling the phantom, i.e., does slight variation in the exact recipe of contrast agent and distilled water result in differences in signal value throughout the phantom. We are also working on protocols which will assess signal drift throughout the field of view in the phantom scans, and assess spatial distortion in the magnetic field. We have obtained 5 3D T1-weighted scans of the phantom, and will use these data to conduct the experiments.

C. Research Assistant
We have hired a new research assistant who will interface with other Consortium members to assist in hardware applications and software use. We chose Aaron Montes (from approximately 40 applicants) who has a bachelor's degree in Behavioral Sciences from Cal Poly Pomona, and has considerable computer expertise and coursework. He has work experience in information technology, and has research experience from his

undergraduate institution. Aaron started work on April 20th, and is in the process of training on the software we propose to distribute to Consortium members.

D. Continued Anatomical Analyses on Existing Imaging Data

We are continuing our collaborative work with Drs. Ed Riley and Sarah Mattson. Our current work is focused on correlating Dr. Mattson's neuropsychological data with the vermal contour data generated by Elizabeth O'Hare (Dr. Sowell's graduate student). Ms. O'Hare has written a brief proposal outlining hypotheses for these analyses, and will be conducting the analyses in hopes of generating an abstract for the upcoming deadline for the Society for Neuroscience. Following is Ms. O'Hare's proposal.

> "The purpose of the present study is to evaluate the neurocognitive correlates of this localized anterior vermis dysmorphology in individuals with prenatal exposure to alcohol. Specifically, we will use the immediate recall subscores on the California Verbal Learning Test for children (CVLT-C) and the Rey-Osterrieth Complex Figure Test (ROCF) as measures of verbal and visuo-spatial memory respectively. As there is evidence to suggest that the cerebellum is important for certain aspects of verbal processing, we predict that the amount of anterior vermis dysmorphology will be negatively correlated with performance on a task of verbal memory (CVLT-C, immediate recall). That is, the more displaced a given subjects' anterior vermis, the worse his or her performance on the immediate recall score of the CVLT-C. Additionally, because both the neuroanatomical and facial phenotypes of PEA subjects appear to be less severe than ALC subjects, we hypothesize that the extent of correlation between anterior vermis dysmorphology and verbal memory performance in PEA subjects will be intermediate to that of unaffected subjects and ALC subjects."

We are also in the process of mapping cerebellar shape abnormalities in these subjects using cerebellar surface renderings and cortical pattern matching techniques.

<u>Dysmorphology Cluster</u>

Ken Jones - Dysmorphology Core:

No report.

Tatiana Foroud – 3-D Facial Imaging:

Since the last conference call, the Facial Imaging Project has moved forward to prepare the cameras for distribution to the various projects encompassing the CIFASD project. Specifically, progress has come in the following areas:

A. Quality Control and Set-up

- A pilot study was completed wherein we reacquired data from 10 of the original pilot study subjects to provide cross calibration assessment with one of the new cameras.
- Further studies were completed comparing the two new cameras that were ordered on the grant. Preliminary analysis shows the cameras are on par with each other with respect to accuracy. These captures are currently undergoing more detailed analysis.
- Finally the AVL worked with Dr. Rick Ward, Dr. Elizabeth Moore and Carol Miller in the process of acquiring a standard model to "calibrate" cameras at remote sites. The model is on order and should arrive in May.
- In addition the AVL assisted Dr. Shiaofen Fang by scanning a plaster dental model provided by Dr. Ken Jones. The scanned data has yet to be merged into a single model. After merging the data will be sent to Dr. Fang for further analysis.

B. Camera Acquisition and Deployment

- The first camera was sent to Buffalo, NY (Luther Robinson). Jeff Rogers then went to Buffalo to help set up the system and refresh Luther and his staff with data collection. Remote support has been scheduled for the month of May. The camera will remain in Buffalo for several months while data is being collected.
- A third camera was ordered with INGEN provided funds. A letter was sent to NIAAA requesting matching funds to provide a 4th camera for the project. No response has been received yet.
- Plans are now underway to get the second camera to Finland for use by Gene Hoyme. The goal is early May.

C. Software Development

- AVL developed a custom plug-in module for the Rapidform software. This module is specifically designed for FAS data point entry, examination and measurement extraction. The alpha version is ready to be deployed to Dr. Elizabeth Moore and Dr. Rick Ward. We are waiting on Dr. Moore's laptop to arrive for software installation. Upon deployment the AVL will train Dr. Moore and Dr. Ward and enhance the interface where requested. Documentation for this plug-in is currently in production.
- The details of the capture protocol documents were updated and are included as a hard copy inside each camera case.
- Andy Arenson and Jeff Rogers met to discuss the XML file format that will be extracted with the Rapidform plug-in and read into the Central Repository. This XML file will contain measurement information and is the essential link between the Imaging Core and Central Repository. The Imaging Core will create one measurement file per scanned subject and the Central Repository will read the data from the file. The AVL is waiting on Andy to finalize the file format. In addition we will add one 3D merged Rapidform file per subject into the repository. This file is meant to be freely available to all participants using the freeware version of Rapidform.

CLINICAL PROJECTS:

Christina Chambers – Assessment of Risk Factors for FASD in the Moscow, Russia:

- The Moscow Region subcontract from UCSD was just written last week and sent to the collaborators. They are ready to start data collection, but just waiting to get funding to do so. The psychologists are scheduled to go through an initial training session by Claire Coles May 26-28, 2004, using the testing battery that was approved by the core.
- Some nutrition and biomarker test kits have required registration with the Russian government to qualify for importation and we are doing that now.
- The administrative core is assisting with a little money to support buying recording equipment for ultrasounds to be archived. I'm throwing another $10K from an Academic Senate grant to support unexpected costs of biomarker kits.
- The ultrasound data collection form went to the bioinformatics core several weeks ago. Final version of the screening form and intake and interim questionnaires, as they will go into the field, will go to the bioinformatics core within the next week (they have the initial version). We're still planning recruitment at the end of next month.
- The Ukraine pilot subcontract from SDSU to UCSD was finalized as of last week (4/19/04). We received notification from SDSU last Thursday that the State Dept. has approved the foreign subcontractor. Now a subcontract needs to be negotiated between UCSD and the Ukrainian American Birth Defects Program before data collection can start

Sarah Mattson - Progress (Moscow, Finland, San Diego)/NB Cluster:

I have been very active since the last conference call. Here is a summary:

A. Test materials:

- We have most, but not all of the materials.
- We are still waiting on the following tests: (the names in parentheses are the person "attached" to it):
- NES-3 (Sarah): we ordered the test and joysticks and are waiting to receive them.
- Reversal shift (Kodi)
- Virtual Water Maze (Ed)
- Barkley Slug (Sarah): I have contacted Rus Barkley about this and apparently it is not a "real" test, it is something used more informally. He suggested I contact some one else who did not get back to me. I can create our own version of the slug if that is what everyone wants.
- The test administration manual is nearly done. We have piloted it and are working out the kinks. We are trying to make it as user friendly as possible. We still need to insert sections on the tests mentioned above. The only other test that is not complete yet in the manual is the calculation test and we are compiling our questions about that and will send those out shortly (to Joe & Sandy). Along with the test administration manual, I will be sending a test administration packet which will have the forms needed to use during administration.

B. Other Reliability Issues

- I sent out an email yesterday on this requesting feedback. If anyone has any comments, please let me know. This email is pasted below.

C. Database
- I have been working with Andy on the database and have been able to send him most of the neurobehavioral measures, with the same exceptions as above.
- I requested information from all the members of the NB core (Kodi, Sandy, Claire, and Åse) but only heard from Åse. Here is the response from them (the Finnish group):
- Thus far we have done the pilot MRS study as well as a short telephone interview with all participants. As we have written earlier we have a group of about 70 FAS/FAE that would be willing to participate. We hope to be able to start calling in the families to the clinic now as Gene is arriving in a couple of weeks.
- We will also be doing a few more MRS examinations during the summer to have enough material - hopefully - for a full article on that. If you need more detailed information - please let me know.

D. <u>Reliability:</u>
- I asked Claire to develop a protocol for increasing reliability between our sites and I am forwarding her proposal, with a few additions from me.
- The issue is the potential for a lack of consistency between sites. This can be due to many factors, including lack of training and familiarity with the tests as well as non-standardized administration. Claire reviewed a grant for the neurobehavioral core on another big collaborative study. They had 4 sites in the US and a number of neuropsych procedures. Apparently, this issue was a huge problem. Even using US trained testers, same language, there were huge intersite differences in administration, outcomes, etc. They wrestled with the issue for years and had to spend a great deal of money on training to get anything useful out of the testing.
- The administration issue will be addressed, at least in part, by the use of the test administration manual that is near completion. The other part of it will be addressed by the use of reliability checks, as described below:
- The proposal is to use a DVD camera to tape 15% of the assessment sessions and have them sent here for reliability checks. The recordings would be reviewed by someone with knowledge in testing and the language. Claire has Russian-speaking colleagues who could help, but we would need to identify others for the other sites. The English-speaking sites will be less of a problem.

E. Advantages:
- That DVDs are easy to send being just CDs; that it will be a way to maintain some standardization in testing and to provide regular feedback to sites and testers. Having such a procedure in place would certainly lend some legitimacy to this procedure and, perhaps, reduce the amount of “spoiled” protocols. Better for getting published. Any reasonable journal will raise these issues.

F. Disadvantages.
- The cost of DVD camera; there would have to be one at each site.
- The cost of the reliability checks; we would have to hire someone to watch tapes and develop scoring system. At least some of the people would have to be fluent in the administration language and trained to identify problems.
- The cost of DVDs and postage.

So far, I have not heard from anyone except the Finnish group who do not like this procedure because they think all the reliability work should be done before the testing begins.

Sandra Jacobson – Identification of FASD in South African Children:

We are currently working in Cape Town with our research team pilot testing the battery of assessments we plan to administer for our 5-year follow-up study of our infant cohort. This battery will include both the age-appropriate assessments agreed upon at the Neurobehavioral Core Meeting held in San Diego as well as several new narrow-band assessments focusing on preschool arithmetic and executive function. We have also included an eye blink conditioning assessment at this age. Our developmental psychologist Andrea Hay came to the US for extensive training in the administration of the newer, more innovative assessments in our laboratory in Detroit as well as at the University of Toronto and the University of Delaware. Pilot testing will continue for the next 2-3 weeks to be followed by initiation of subject testing. We have

also included an in-depth maternal interview for collection of potential confounding variables that were discussed in San Diego. We are also in the process of arranging for blood draws to assess ADH2 polymorphisms in the mothers and children and lead exposure and iron deficiency anemia in the children.

Phil May - South African, Plains Project:

No report.

BASIC SCIENCE PROJECTS:

Keith Miller –Photolabeling of Alcohol Binding Sites:

No significant breakthroughs since last update.

Charles Goodlett – Testing FASD Therapeutic Agents in Neonatal Rodent Models:

- Paper on caspase-3 active subunit expression as a marker of acute cerebellar cell death and lack of effect of vitamin E in protecting against cerebellar cell death under review in ACER; reviews expected this week.
- Initiation of ethanol dose-response analysis of eyeblink trace conditioning. Preliminary data indicate that 5 g/kg of ethanol per day (postnatal days 4-9), but not 4 or 3 g/kg per day, induces significant (and large) deficits on trace conditioning, a hippocampal-dependent form of learning. This will allow us to assess functional protection of L-NAP in hippocampal-dependent learning (trace conditioning), to go along with neuroprotection studies of cerebellar-dependent learning (short-delay conditioning).
- Research microscope purchased to dedicate for cell counting and fluorescence and bright-field imaging of L-NAP neuroprotection.
- First pregnant rats obtained for L-NAP studies; dosing and analysis of neuroprotection against cerebellar cell death in May and June.
- We have continuing L-NAP study with prenatal alcohol liquid diet model on C57BL/6 mice, the L-NAP is further demonstrated to protect against the alcohol reduced body weight and brain weight at E15 embryos. The embryonic body weight in alcohol and L-NAP treated embryos increases from the level of alcohol treated group, but is lower than those of pair-fed and chow fed group. The brain weight of alcohol and L-NAP treated embryos increases from the level of alcohol treated mice and reach to the levels of pair-fed and Chow-fed controls.
- On postnatal study with C57BL/6 mice, we continue in verifying the effect of alcohol on apoptosis of forebrain neurons, particularly limbic and hippocampal neurons with Caspase-3 immunocytochemisty. We expect to report on binge-drinking on apoptosis of forebrain neurons at P 7.
- The following paper supported from the current grant was submitted to the Journal of Molecular Neuroscience and being accepted:
  Zhou, F.C., Sari, Y, Powrozek, T, and Spong, CY, A Neuroprotective Peptide Antagonizes Fetal Alcohol Exposure Compromised Brain Growth, J. Mol. Neurosci,

We evaluated a nine amino acid peptide, SALLRSIPA (SAL), an agonist of Activity Dependent Neurotrophic Factor (ADNF), for its protective properties against fetal alcohol related brain growth retardation, using an established liquid diet model of alcohol-related neurodevelopmental disorder (ARND) in C57BL/6 mice. Alcohol exposure during neurulation reduced body weight, head size, and specifically brain weight and volume. Major gross brain deficits include underdevelopment of brain areas, cortical thinning, ventricle enlargement, and restricted midline neural tissue growth leading to openings at the roof /floor plate. SAL treatment increased the fetal body weight and restored the brain weight, brain volume, and regional brain size. Furthermore, SAL restored the cortical thickness, reduced the size and frequency of neural tube openings, and attenuated ventricular enlargement. The ability of SAL to antagonize alcohol-retarded brain growth and development of forebrain and midline neural tube at midgestation suggests its potential use as an antagonist against fetal alcohol rendered microencephaly early in development.