



# The MFMU Networker

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## Network Protocols Prioritized

Armed with the input from each center's prioritization of approved Network protocols in the queue, the prioritization subcommittee met by conference call to discuss the initiation of two studies. "A Randomized Trial of 17 Alpha-Hydroprogesterone-Caproate for Prevention of Preterm Birth in Multifetal Gestation" and "A Randomized Trial of Omega-3 Fatty Acid Supplementation to Prevent Preterm Birth in Pregnancies at High Risk" were voted for implementation. It is the wish of the NICHD to have both trials up and running by the end of the year.

A draft of the progesterone/twins protocol has been distributed to the PIs for comments that will be incorporated by the primary investigators, Drs. Caritis and Rouse, when they present the study at the July Steering Committee meeting. On July 7, Drs. Margaret Harper, Paul Meis, Elizabeth Thom and Valerija Momirova, MS will be site visiting Ross Laboratories in Columbus, Ohio. On the agenda will be a taste testing of potential formulations, discussion of protocol design issues and a panel discussion of problems of preterm delivery with Ross scientists. The BCC has brought the protocols for both projects in-house to begin work on them.

## NICHD Reorganizes CRMC

Three of the six branches that were under the Center for Research for Mothers and Children Division (CRMC) of NICHD have been assigned to a new center called the Center for Developmental Biology and Perinatal Medicine (CDBPM). The Pregnancy and Perinatology Branch, of which Dr. Cathy Spong is Chief and under which the MFMU Network exists, has been assigned to this new center. Dr. Jim Hanson has been named Acting Director and Dr. Charlotte Catz is the Acting Deputy Director.

## Screening Begins for Capps

The first four centers (Ohio State, Case Western, Northwestern and UNC) that have been certified began screening patients for the CAPPs trial during the week of June 15, and several patients have consented to the compliance run-in. The McKay Dee site at Utah and Wayne State were certified June 26. Most of the remaining centers have submitted all the requirements for certification and should be screening very shortly. Many components of the trial finally came together in early June, including decisions about the number of visits and amount of blood draws, compliance testing, study medications and IRB approvals.

Paul Thadikonda of Eminent Services, the supplier of the study drug for the trial, has succeeded in overcoming a number of challenges in the production of the drug. After the first of the year when he was asked to provide the drug after the potential supplier was not able to cooperate with FDA regulation, Dr. Thadikonda had to find a manufacturer that could combine vitamins C and E in one capsule. He found the manufacturer, Strides, Inc., in New Jersey and worked on specifications and production standards that are required for the IND submission for the FDA.

Within a couple of weeks after the IND was submitted, both firms were visited by FDA auditors and were required to respond to a number of inquiries. Meanwhile, Dr. Thadikonda, while visiting Strides for the initial production run, discovered that the black capsules did not conceal the substances when held up to the light. One was opaque while the other could be seen through. He quickly went back to the drawing board and found that adding titanium dioxide to the mineral oil produced a cloudy substance. Revisions were sent to the FDA, which readily approved the addition since it is well below any kind of safety level. He also found a different gel capsule to use, which is smaller than the black one and is brown in color. This necessitated creating a different size blister pack, which initially was cut by hand until a new machine was purchased, for packaging the drug.

Finally, Dr. Thadikonda was able to mail the compliance drug June 12 and the study drug on June 18. The final protocol, manual of operations and most of the data forms were mailed on June 13. The remaining data forms will be sent shortly. A revised manual will be sent, incorporating the Prediction study, once it is implemented. Centers will order new study drug when they have one box (containing 8 patient study kits) remaining by contacting the BCC.

Meanwhile, work continues on the Prediction part of the protocol, including exactly which assays will be used. A number of outside experts have been consulted and the investigators currently are considering the options. The main difference between the RCT and Prediction studies is the amount of blood drawn at visits and the addition of physical measurements and uterine doppler in the Prediction study.

## NEJM Progesterone Article Elicits More Publicity

Following the June 12<sup>th</sup> issue of the New England Journal of Medicine which published the results of the 17-alpha-hydroxyprogesterone caproate (progesterone) trial, there has been a flurry of articles in the media. Dr. Cathy Spong was being bombarded with callers and interviewed by NBC radio, and Drs. Meis, Peaceman, and Varner were among the PIs quoted in papers such as *The New York Times*, *USA Today*, *Wall Street Journal*, *The Denver Post* and by ABC News.

One of the frustrating aspects of this trial, which advocates prescribing progesterone for women who have previously had a very premature delivery, is that the injections are not commercially available. ACOG is favorable toward the results but can't (cont'd p.2)

**(Progesterone Article cont'd)**

endorse the treatment because it is not widely available. While one pharmaceutical firm (Wedgewood) makes the injection, they do not have FDA approval to ship it over state lines.

Several investigators have commented that more study needs to be done to replicate the results and to see if there are any long-term effects on the babies. Meanwhile, a similar study in Brazil has found daily vaginal suppositories of progesterone cut premature births by half.

## Corticosteroid Trial Stopped by NICHD

Following the recommendation of the Data and Safety Monitoring Committee, which met March 20, Dr. Duane Alexander and the NICHD halted recruitment into the Network's trial of Antenatal Corticosteroid Regimens. The DSMC previously had cited concerns over slow recruitment and, though recruitment had increased since the last review, the committee noted that it would still take at least six years at the current recruitment rate to complete the trial. Patients who were already enrolled were permitted to complete their study medication. The infant follow-up component of the trial also will continue, following the endorsement of the committee.

Recruitment began in the spring of 2000 and was expected to take three years to reach the sample size of 2400. When the trial was ended last March, a total of 495 patients had been enrolled.

While the last delivery is not expected until the first week of July, the BCC is working diligently to get the data together and cleaned up in time to submit an abstract to SMFM. Speedy data entry and quick turn around of edits and audits by the centers are very much appreciated. A review of neonatal cranial ultrasounds was held in June and the final one is scheduled for July 10. Dr. Susan McCune, a neonatologist who was hired as a consultant to review charts for primary outcome, also has been hard at work validating the primary outcome.

## MFMU Network Web Site Revamped

A redesigned web site for the Network was launched June 5, incorporating a number of new functions with plans to implement new ones over the next few months. One of the new options includes a searchable Rolodex with each center responsible for keeping their own contact information up to date. In fact, it is recommended that coordinators check their center information now and make changes as required. In addition, members can create and manage conference calls, and refer to a detailed event specific calendar and FAQ center. The site containing information for public use remains the same.

Each user now is required to have their own userid and password and will need to change their password every six months or so for security reasons. This new procedure will also allow us to soon implement another useful function, an online manuscript editing process. The web address remains the same:

[www.bsc.gwu.edu/mfm](http://www.bsc.gwu.edu/mfm). Please call Kevin Pinder (301-881-9260) if you encounter any problems or have questions.

## SMFM Abstracts in Production

A total of 23 abstracts are being worked on for submission to SMFM. The proposed list was prioritized by study and topic on a Publications Subcommittee call May 30. Most investigators should receive their data from the BCC no later than July 17. Each abstract needs to be submitted to Dr. Brian Mercer, Chair of Publications by Noon on August 1. A conference call will be held August 5 at 10:00 AM to review and comment on all abstracts. Investigators are encouraged to participate to receive feedback. Final abstracts need to be electronically submitted to the SMFM office by August 8.

As a reminder, all investigators, except those conducting primary analyses, must get IRB approval for their secondary analysis and send it to the BCC before the BCC can release data to them.

## FOX Update

Between March and April, recruitment went up by 40 patients, while April to May remained flat. However, recruitment in June looks like it has improved again. Much of this is due to big increases at Magee-Womens, Wake Forest and Houston!

Several modifications to the laptop software were sent to all the centers on June 24, which should minimize some problems occurring with the laptop. One modification prompts for a confirmation of the date and time of randomization. Another prevents the computer from turning off when the lid is closed. A utility was also written so research staff can look up randomization codes for enrolled patients given the screening number.

Several other potential problems have been observed in the software and hardware that cannot be replicated on the equipment at the BCC. Thus, plans are being made for Steve Weiner, Angela Swanson and Brendan Broderick from the BCC and Sandy Weininger from the FDA to visit UTSW August 18. There they will investigate whether the problems are specific to the software or the way the hardware is being operated. In addition, an error log has been sent to centers to be used for each unit to document problems, including error messages appearing on the screen and the actions that were taken to resolve the problem. These logs should be sent to Angela Swanson each Friday regardless of whether problems are observed or not.

## U/S Quality Problems Continue

Ultrasounds from both the BEAM and BEARS studies continue to be erratic in quality. The films from the last U/S review are being returned to centers with those of poor quality separated from the rest. Coordinators have been asked to show these films to their radiology department. If the images are poor quality because of the reproduction process, they should request new copies and send them to the BCC.

### Cathy Craven

With great sadness, we pass on the news that Dr. Cathy Craven, a pathologist associated with the University of Utah who was working on placental pathology for the Factor V Leiden and corticosteroids studies, passed away on April 1 as the result of an automobile accident. At the time of her death she was commuting to Cedar City where she worked as Head of the Pathology Department at Valley View Medical Center.

Shortly before, Cathy had indicated to NICHD that she no longer had time to work on the Network studies and wanted to relinquish her responsibilities. Though some plans about how this would be done were being discussed, no decisions had been made. Recently, NICHD asked the Network PIs to nominate a pathologist at their center who would be interested in participating, perhaps as part of a placental pathology working group. Several responses have been sent to Dr. Spong and options are being considered.

## Another Amazing BEAM Tale of Follow-Up

The Network's BEAM trial is maintaining a very high percentage of successful infant follow-up, which entails visits at 6, 12 and 24 months. The follow-up is necessary to ascertain the primary outcome of the study, which is cerebral palsy. There has been a long string of surprising tales about long-lost study participants finally being found. The following story was related by BEAM follow-up coordinator, Lisa Fullmer at Utah.

The BEAM patient was born in June 2001 and never returned for a study visit. Lisa knew where the mom lived (with the grandmother) and called and stopped by several times. The grandmother persisted in telling her that the baby's father refused to let the baby be examined for the study. Lisa even played outside with the baby on one of her visits. Eventually the grandmother gave the father's phone number to her. After several calls to the father's phone, she eventually spoke with an older man who identified himself as the father's uncle. He told her that the father, along with the baby, were living with him. On a recent Sunday Lisa called several times and the father finally returned her call because he was curious about whose number kept appearing on his caller-id.

Lisa explained the reason for her call and discovered that the baby has been living with him, at his aunt and uncle's, since the baby was six weeks old. At this point, she realized that the baby she played with at the mother's house was not the patient. The father asked Lisa if she knew his aunt who is a nurse at the hospital. It turned out that she knew his aunt well and that they had worked together for 20 years! The baby was in for her first follow-up exam the very next week. Finally, with much effort and determination for almost 2 years, Lisa succeeded in getting an infant back for the essential study visit!

## Garland Anderson Named New Chair of Network

Garland Anderson, MD, has been named Chair of the MFMU Network following the resignation of Dr. Steven Gabbe, Dean of the School of Medicine at Vanderbilt. Dr. Anderson has been the Chair of the Department of Ob/Gyn at the University of Texas Medical Branch at Galveston for fourteen years. His special emphasis in maternal-fetal medicine is on hypertensive disorders of pregnancy. He is known for building UTMB's Ob/Gyn department into a strong academic facility with a fellowship program and faculty committed to quality research and fellowships. Dr. Garland has personally mentored a MFM fellow each of his 14 years at UTMB.

He also has been recognized by his institution for his administrative ability while serving as Chair of UTMB's Medical Service, Research and Development Plan, which included managing outpatient clinics, the central billing system and physician contracting. For those accomplishments, he was awarded the Nicholas and Katherine Leone Award for Administrative Excellence in 1994, the only Chair at UTMB to win this award in the last 14 years. He currently is the PI on the UTMB WRHR Career Development Center of Excellence sponsored by NICHD.

Dr. Anderson received his medical degree from the University of Tennessee, did his internship at Hermann Hospital in Houston, was a resident at UT-Houston and a Fellow at the University of Louisville, Kentucky. He is a past President of SMFM (1992), among many other positions and professional memberships, and has received numerous honors, including being named in "The Best Doctors in America" and Good Housekeeping magazine's "Best Doctors for Women". He is the recipient of many research grants and contracts, resulting in numerous papers and presentations. His most recent award was received at the 2003 Annual Meeting of SMFM where he was the recipient of the SMFM Award for Research Excellence for his research, "On the fetal origin of disease: Effect of uterine environment and genetic imprinting on vascular reactivity in later life."

## People in the News

- ◆ **Maureen Hoover** has announced her resignation as RA on the BEAM trial. She has been accepted to the doctorate program at UNC-Chapel Hill in Reproductive Epidemiology. (Perhaps we'll see her name in the field of maternal fetal medicine research again someday!). She will be leaving mid-August to pursue her studies. **Angela Swanson** also announced that she will be leaving this fall. She recently was engaged to be married and wants to return to the Boulder/Denver area to be nearer family. She received her undergraduate degree from CU and misses the big outdoors and lifestyle of the West. Her fiance just received his MBA so they are both job searching in that area.
- ◆ The BCC has hired two new Research Assistants: **Barbara Jones-Binns** and **Rayna Matsuno**. Barbara has a degree in biology from the University of Maryland and will be receiving a BS in Computer Science this December, also from Maryland. She describes herself as an army brat, having lived all over, but calls Maryland home after 18 years here. Besides getting another degree this December, Barbara will also become a first time mother. Barbara previously worked as a case manager for a health care consultant, where she did independent reviews for health plans and state mandated appeals. Barbara is taking over as RA for the BEAM study and is receiving excellent training from Maureen.
- ◆ **Rayna Matsuno** recently graduated with a degree in biochemistry from the University of Washington. She arrived in Washington last fall and, because of her interest in cancer, found a job with the National Cancer Institute's Cancer Therapy and Evaluation Program. While at U of W, she enjoyed running and conductin lab research on supported lipid monolayers. She plans to pursue a MPH degree. Rayna was born in Korea, spent her first few years in Hawaii, but grew up in Japan. In her spare time she enjoys playing the piano, reading, and swimming. She will be working as the RA on the new progesterone/twins study.
- ◆ We welcome **William Noble, PhD**, Associate Research Professor, who recently joined the GWU Biostatistics Center as the Alternate PI for the MFMU Network. Bill also will work on other projects at the BCC, including being the PI on the Medical Therapy of Prostatic Symptoms trial. He is beginning by getting his feet wet working on a number of abstracts for SMFM. He has a BA and MS in applied mathematics (Berkeley and University of Missouri) and a PhD in Statistics from Michigan State University. For the past four years he has been at MedImmune, Inc., where he was the lead statistician for Rheumatoid Arthritis (Phase I/II), Respiratory Syncytial Virus (Phase I/IV), and Human Papillomavirus (Phase I/II) programs. He also worked for Parke-Davis Pharmaceutical Research on Phase III Infectious Disease studies and Phase II Central Nervous System studies. Bill also has extensive teaching experience and has published numerous clinical study reports and other publications and presentations. He has a daughter and son, both attending the University of Maryland, and enjoys running and baking bread.

## A Salivating Story

Paul Meis, M.D.

Ever wonder what happened to all the thousands of saliva samples that we sent to Biex in California from the progesterone study? Here is the story!

The Biex Corporation went bust in early 2001 and all of its assets were disposed of, including (almost) our samples of saliva. However, a resourceful research nurse practitioner, Cheryl Hastings, a former employee of Biex, came to the rescue. She gathered up all of the salivary samples and placed them in a freezer in the corner of a friend's laboratory. There they remained, unknown to us, for two years. In the meantime, further samples that were being collected from patients enrolled in the study, were kept at the MFMU Centers.

At the time of the Opening Reception at the SMFM meeting in San Francisco in February, we saw Cheryl and she told us that the samples were located nearby and that she could help us retrieve them. At about this time the Adeza Corporation became interested in acquiring the assets of Biex. Adeza was also in contact with Cheryl and wanted to retain the samples. We thought this was not the best idea, and that all of

the samples needed to be collected in Rockville to be cataloged by McKesson Bioservices so we then could make decisions about assays. We convinced Adeza that 1) they did not have all of the samples, 2) some of these samples were from the first iteration of the progesterone trial and were not usable, and 3) the samples were the property of the NICHD. Adeza reluctantly agreed to release the samples and we made plans to go rescue them from the freezer in Sunnydale.

We set a date to meet with Cheryl. She flew from Colorado, and I from Winston-Salem, and we met at the San Francisco airport. When I arrived, Cheryl told me of a new complication. The owner of the lab where the freezer was located complained that Biex owed him money and he wanted to get paid before releasing any of their assets! However, upon meeting the gentleman, he was quite cordial. We explained that Biex owed us money as well, and that the samples were the property of the NIH. He not only released the samples, but donated three Styrofoam containers for shipping. After purchasing 35 pounds of dry ice, (that's a COLD load), we

packaged up the samples and took them to a UPS store. We (naively) listed the samples as biological fluids, which immediately aroused the shipping clerk. She insisted that we open the container to show her the triple sealed samples, and she then looked up UPS regulations. She told us that they would require special UPS plastic bags for each individual sample box. We thanked her and left. We next went to a Fed EX store where they took the samples without any questions.

The samples now reside in Rockville where they are being cataloged. Adeza remains interested in performing the assays, but no contract or commitment has been made.

A further twist in this story is that the freezer in Sunnydale was a frost-free model, meaning that the samples were subjected to freeze-thaw cycles. Biex also had some of their standards in the same freezer, and Adeza plans to assay these standards in the next several weeks to determine if any deterioration occurred.

We will keep you posted about further developments!

## MFMU CALENDAR



### Steering Committee Meetings

- July 14-15, 2003
- October 23-24, 2003
- January 22-23, 2004
- April 15-16, 2004
- July 12-13, 2004
- October 21-22, 2004

### Important SMFM Dates

- Deadline for SMFM abstract submission to Dr. Mercer: August 1, Noon
- Publications Subcommittee SMFM Conference Call: August 5, 10 AM
- Deadline for abstract submission to SMFM: August 8

### Society for Clinical Trials Annual Meeting

- July 20-24, 2003, London, England