

## Network Prioritizes Next Study

In April, the Network's Prioritization Committee convened by conference call to discuss the results of the votes from the members of the Steering Committee to prioritize the existing protocols in the queue. Eight protocols have been approved over time by the Steering Committee, but have not yet been implemented. Of the three considered most scientifically or clinically important, timely, and with the probability of changing clinical practice, the committee decided that the "Randomized, Placebo Controlled Trial of Thyroxine Therapy for Subclinical Hypothyroidism Diagnosed During Pregnancy" would be the next to move ahead.

Over the past couple of decades, research has found that deficiency of the thyroid hormone in the mother leads to fetal hypothyroxinemia and can be one cause of poor neurodevelopmental outcome in her offspring. Women who are found to have elevated TSH levels and free T<sub>4</sub> values below the reference range currently are diagnosed to have "overt hypothyroidism" and are treated with thyroxine (synthetic thyroid). The few studies that have been done regarding the identification of thyroid deficiency, the timing of treatment and the impact on neonatal and infant development have led to conflicting and confusing positions about whether or not *all* pregnant women should be screened for hypothyroidism and treatment also prescribed for those found to have elevated TSH levels but normal free T<sub>4</sub> levels (subclinical hypothyroidism). There have been no intervention trials to examine the risks and benefits of treating maternal subclinical hypothyroidism.

Regardless, this past January, the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE) and the Endocrine Society released a consensus statement recommending routine TSH testing during pregnancy. The economic impact of screening all pregnant women would be enormous. There are about 4 million births annually in the U.S. Approximately 2.3% pregnancies (100,000 women) are affected by subclinical hypothyroidism and 0.2% are diagnosed with the overt disease annually. Depending on the cost of screening - which can be as high as \$500 per patient - the total cost to detect hypothyroidism could be \$2 billion per year.

Co-investigators, Drs. Brian Casey and Ken Leveno from UT Southwestern, have developed a trial to determine whether women who are diagnosed with subclinical hypothyroidism during the first half of pregnancy and are treated with thyroxine results in a decreased risk of intellectual impairment in their offspring at age 5 years using the Wechsler Intelligence scales. The Advisory Board met by conference call on June 7 and enthusiastically supported the protocol. The first meeting with the BCC to work on details of the study protocol will occur June 28. The next meeting, which will involve the entire hypothyroid subcommittee, will occur July 20, prior to the Steering Committee meeting.



## Recruitment Soars for Network's Newest Trials

Both the STTARS and Omega-3 trials are recruiting faster than originally estimated. For the Omega-3 trial, the goal was to randomize 19 patients per month. Though the trial only got off the ground in January, the month of May saw 41 patients recruited and, as of June 10, 102 patients out of the of 800 sample size had been randomized. Similarly, it

was expected that about 15 patients per month would be randomized into the STTARS trial. However, recruitment is averaging about 35 patients a month. The STTARS trial now has 420 patients randomized of the 700 needed.

The earlier Network trial which showed that progesterone reduced the risk of preterm delivery in women

## Publications On A Roll

In the first six months of this year, the Network has had 12 manuscripts either published or accepted for publication! Eight others are in various stages of review.

The new on-line manuscript review and editing process seems to be working very well. Collaborating investigators, subcommittee members and reviewers are able to read, critique and edit the most recent version of a manuscript on the MFMU website and then, after selecting suggested changes, the author uploads his next version for reviewers to check.

As investigators become more familiar with this process, the system should become even more efficient. The BCC is happy to receive feedback if anyone has comments.

## Placentas Available for Research

There are about 700 placental specimens from the BEARS and Factor V Leiden studies available for research proposals. The data from the gross examination of 329 FVL placentas and 151 BEARS placentas currently reside at the BCC. An additional 224 placentas from the BEARS trial still need to be evaluated.

The NICHD MFMU Network is encouraging the submission of proposals for how to best make use of these resources for research. Proposals should be sent to Dr. Spong at the NICHD and Dr. Thom at the BCC by July 15.

with a previous preterm delivery may account for patients being eager to enroll in these trials. The women in the STTARS trial have multifetal pregnancies which have a high risk of early delivery and, by participating in this trial, they have a 50 percent chance of receiving progesterone (the rest get placebo). The purpose of the Omega-3 trial is to see whether or not giving Omega-3, a nutritional supplement, in addition to progesterone, further decreases the rate of preterm birth in women have had a previous preterm delivery. In this trial, all pregnant women are given progesterone and randomized to receive either Omega-3 or placebo. The progesterone in both studies has the same formulation as the

original trial.

The manuals for both studies are being updated to clarify some issues and to reflect some minor changes in procedures. Network nurses should make sure to review these changes when the revised manuals are released. Additionally, the Omega-3 study drugs will be recalled and replaced in August because they will be expiring. A presentation will be made at the July meeting on how this will be done.



**Clean-up Continues on FOX Trial**

Data clean-up is almost complete for the FOX trial although charts continue to be reviewed by Drs. Bloom and Spong for various secondary outcomes. It is expected that the manuscript will be completed for submission to a journal in August.

Clinical centers were asked to submit justifications for keeping any of the FOX equipment if they had a use for it (laptops, GE fetal heart rate monitors and N400 oximeters). Requests have been received and the centers will soon be notified about the distribution. Centers will be allowed to keep the oximeters they currently have. Some fetal heart rate monitors remain unspoken for and may still be requested from the BCC. Those centers requesting laptops will receive at least one. Coordinators will pick up their laptops at the July Steering Committee meeting.

**CAPPS RCT Reaches Monthly Target**

Recruitment into the CAPPS trial exceeded its monthly goal of 280 patients per month in March 2005, and has come close to that number every month since. As of May 31, 3,293 of the 10,000 sample size have been randomized. However, the percentage of patients who have been declared lost to follow-up has crept disturbingly high such that, if the trend continues, the ability to determine a treatment effect at the end of the study could be threatened. The Network goal for antepartum trials without long-term follow-up is to keep the lost to follow-up rate under 2 percent which has been successfully achieved on almost all studies to date. The current rate for CAPPS is over 4 percent. Research staff have been asked to make every effort to retrieve delivery data previously declared missing.

All CAPPS study medications will be recalled and replaced at the end of July. While vitamins are not given expiration dates, it is generally accepted that after two years they lose their potency. The BCC and Eminent will plan an orderly recall procedure and the coordinators will be given instructions at their meeting in July.

Meanwhile, recruitment into the Prediction study lags. Since less than 40% of the patients are being

randomized into the CAPPS RCT prior to 13 weeks, this means that nearly everyone who qualifies for the Prediction study needs to grant consent in order to reach the sample size of 4,000.

The protocol subcommittee plans to begin identifying additional assays for the specimens collected from patients.

**Progesterone Follow-up Study Proceeding Slowly**

The follow-up of infants who were born while their mothers were on the original Progesterone trial has been taking longer than expected. In part this may be due to the windows of time the child is eligible to complete the Ages and Stages Questionnaire (ASQ) exam which become further apart as the child ages.

Research staff are encouraged to contact and set up appointments for the ASQ and exam immediately. All offspring must have the exam before reaching 5 years three months of age. As of May 31, 149 patients have been enrolled, two have refused and 197 patients still need to grant consent.

**BEAM Trial Continues with Infant Follow-up**

Accomplishing infant follow-up at 6, 12 and 24 months continues to

challenge many of the clinical centers. Strategizing conference call "site visits" have been held with centers that are struggling to get their patients to return. A form letter encouraging patients to have their follow-up visit has been drafted by Dr. Carpenter and is available for centers to use.

The last full central review of cranial ultrasounds will be held the Children's National Medical Center in Washington, D.C. on September 21 and 22. The BCC has been requesting new copies of ultrasounds that have been sent in previously by some centers but were of such poor quality they could not be read. It is hoped that the clinical centers will comply with the request so that these patients can still be evaluated.

Terry Leach continues to certify the Bayley examiners who need to remember to submit their tapes to her. There will be no further training for follow-up examiners at the Kennedy Krieger Institute. However, tapes of follow-up exams will continue to be reviewed for certification by Dr. Bruce Shapiro.

Data close-out for the trial is scheduled for December 2006. Meanwhile, a subcommittee meeting will take place at the July Steering Committee meeting to determine what assays should be run on the specimens remaining from the trial.

## The Cost of IRBs Studied

A letter to the Editor in the April 28, 2005 issue of the *New England Journal of Medicine* reported on a study conducted in 2002 by the Consortium to Evaluate Clinical Research Ethics. Approximately half of the 121 U.S. medical schools surveyed completed the survey which included information about the composition, costs, and other various activities of Institutional Review Boards. The purpose of the study was to evaluate whether IRBS have sufficient resources to fulfill their responsibilities for protecting human research participants.

The study found that low-volume institutions (less than 350 new protocols per year) had an average of 6 IRB staff members and high-volume institutions (700 or more new protocols per year) had 14. The mean number of IRB panels was 1.8 in low volume institutions and 4.1 in high volume institutions. Forty-three percent of institutions provided no financial support to IRB members. Fifteen percent of centers outsourced anywhere from 2 to 378 protocols annually and forty-one percent of new protocols underwent expedited review.

The largest amount of IRB staff time (29%) was spent on general administration and the least amount of time (5%) was spent on conflicts of interest. IRB members' time was spent in various ways. Chairs and vice-chairs spent more than half their time on review and approval of protocols.

The median amount of money spent by academic medical centers on IRBs was about \$750,000 per year, which is more than previously estimated. The more protocols that were reviewed, the less it cost to review each one. Expedited review was used quite frequently but it still cost about the same as full protocol review. This may be because expedited reviews are conducted by IRB members who are more highly compensated than other members.

## Scientists Admit in National Study to Misconduct

The June 8<sup>th</sup> issue of the *Washington Post* reported on the first study of scientific misbehavior, conducted by the HealthPartner Research Foundation, and published in the journal *Nature*. The 3,247 anonymous responses from a survey sent to thousands of scientists who are funded by the NIH indicated that more than 5 percent of scientists toss out data because the information contradicted their previous research or said they had circumvented some human research protections. Ten percent admitted they inappropriately included their names or those of others as authors on published research reports. More than 15 percent admitted they had changed a study's design or results to satisfy a sponsor or ignored observations because they felt they were not right. None of these activities qualify as outright scientific misconduct under the strict definition used by federal regulators.

Definitions of acceptable behavior have shifted so it is difficult to determine the prevalence of research misconduct. Five years ago, the issue was addressed when the Office of Research Integrity at the Department of Health and Human processes.

## Technology Corner

► The MFMU's web site has a new look and provides more information for the public who access it. One of the major changes is that it now includes recruiting information (approved by the GWU IRB) for current studies and provides direct links to the nurse coordinators at each center.

► Another new enhancement is that the weekly edits are now e-mailed individually by each research assistant to designated staff at each center. No longer are the edits faxed all at one time on Friday. Some may now arrive as early as Thursday, giving center staff additional time to respond by the following Wednesday. This follows the recent change from Fed Ex mailing to e-mailing of the monthly reports to the principal investigators.

► Investigators should remember to use the new email address when submitting proposed analyses: [MFMUPROP@Biostat.bsc.gwu.edu](mailto:MFMUPROP@Biostat.bsc.gwu.edu). This address is a repository for proposals only; it is not used for comments or communications regarding analyses. Investigators should send their proposals to this e-mail address ONLY. The BCC will coordinate dissemination to the correct protocol subcommittee chairs.

► The March of Dimes Perinatal Data Center has redesigned its Web site. This Spring it highlights the latest research from the Perinatal Data Center, announces newly integrated PubMed literature searches and describes the latest data updates on the Web site. The address is: [www.marchofdimes.com/peristats/](http://www.marchofdimes.com/peristats/).

Services defined research misconduct as "fabrication, falsification or plagiarism in proposing, or reviewing research, or in reporting research results". About a dozen federally-funded scientists are found each year to have breached that standard with punishment generally being a ban on further federal grants.

In the study's survey, 0.3 percent admitted to faking research data and 1.4 admitted to plagiarism. Lesser violations were more common, including 4.7 percent who admitted to publishing the same data in two or more publications to beef up their resumes, and 13.5 percent who used research designs they knew would not give accurate results.

The investigators who conducted the research feel that much of the scientific misconduct is the result of frustrations and injustices built into the modern system of scientific awards. A preliminary analysis of other questions in the survey suggests that there may be a link between misconduct and the extent to which scientists feel the system of peer review for grants and advancement is unfair. The researchers say that this suggests that those systems need to be brought up to date with current processes.

## People in the News

The BCC has said goodbye to two research assistants, **Rob Blanchard** and **Adrienne Arrieta**. Rob left to work with his wife at the U.S. Agency for International Development (USAID) where he can use his knowledge and talents to work on developmental programs for African countries. Adrienne is continuing to work on clinical trials as a statistician at the Children’s National Children’s Medical Center here in Washington, D.C.

● **Caroline Cobb** has been hired by the BCC as a research assistant to take over the GDM trial. Hailing from Richmond, Virginia, she recently graduated from the American University with a degree in psychology. Prior to coming to the BCC she worked at the Behavioral Pharmacology & Health Promotion Laboratory on psychological studies dealing with tobacco and drug dependence. While there she screened and processed patients and assisted in analyses. Her hobbies include horse training and riding, and writing, singing and playing the piano.

● **Jennifer Cromwell** is another new research assistant who will be working on the Omega-3 trial. She is originally from Washington State but attended Bowdoin College in Maine where she got a BA in Government (international relations division) and French with an Economics minor. She since has attained her M.A. in International Development Studies and is a candidate for an MPH in Epidemiology, both at GWU. She has been working at the National Association of Public Hospitals and has other experience in both national and international research projects concerning reproductive health, family planning, health disparities and women’s issues, including the legal, economic and social rights of women in Morocco.

● **Dr. Maggie Harper** is proud to announce that she delivered the first patient she randomized to the Omega-3 trial at 40 weeks, 3 days on June 15. Baby weighed in at 7 lbs, 15 oz!

## Above and Beyond...

Dedication toward their work continues to be demonstrated by Network Coordinators. According to Missy Swain, the coordinator at Wake Forest, Karen Dorman, the coordinator at Chapel Hill, got to work one morning recently and realized that Fed Ex had not picked-up the cytokine sample from an Omega-3 patient that she had prepared for shipping the previous day.

Knowing that the specimen had to be processed by the lab within 24 hours of collection, Karen rallied Sean Calfee,

their great Data Entry Specialist/All ‘Round Can-Do person to drive the sample to the lab that is located two hours away at Wake Forest.

Missy met Sean at the agreed upon drop off spot and he handed the box to her through the car window. In return she gave him an item to be returned to Karen, along with a number of shipping boxes that are being recycled. Never leaving the car, Sean sped off to return to Chapel Hill and his other duties. So the sample was saved and Network teamwork prevailed!

## And the Winner is...

**Dr. Brian Mercer**, PI at Case Western, beat UTSW nurse Andrea Casteel by only 18 hours with the first correct response to the Brain Teaser Contest in the March *Networker*.

### June 2005 Puzzler

This month you are playing Su Doku, the hottest new game in England. Doku has been played in Japan for years, though the puzzle was originally created by Euler, an 18<sup>th</sup> century mathematician. Since the first puzzle appeared in London in The Times on November 12, 2004, thousands enter the newspaper’s competition each day. No mathematics are required – have fun and good luck!

#### HOW TO PLAY

To solve a Su Doku puzzle, every digit from 1 to 9 must appear in each of the nine vertical columns, in each of the nine horizontal rows, and in each of the nine boxes. They range in difficulty from easy to very hard, depending on the positioning of the numbers you’re given to start with.

#### MEDIUM

5	7		1		4	8
	2				6	
9			6	2		7
			4	9		
	4				2	
			1	5		
7			3	4		1
	3				5	
6	1		9		3	4

Hint: There can only be one of each number 1-9 in each column, each row and each 9-cell square.

## MFMU CALENDAR

### 2005 – 2006 Steering Committee Meetings

July 21-22, 2005                      April 27-28, 2006  
 October 27-28, 2005                July 20-21, 2006  
 January 19-20, 2006                October 19-20, 2006

### Professional Meetings

SMFM.....January 30-February 4, 2006, Miami, FL  
 SGI.....March 22-25, 2006, Toronto, Canada

### Site Visits

Wayne State University                      July 14-15, 2005  
 University of Texas – Houston.....Date TBD

### Publications Deadlines for SMFM 2006 Annual Meetings

Proposed SGI abstracts to Publications.....June 15, 2005  
 Deadline for submission to SMFM 06.....August 5, 2005  
 2004 SMFM manuscripts completed.....October 30, 2005  
 2006 SMFM manuscripts completed....December 15, 2005