

APEX Protocol Revised



The PIs of the MFMU Steering Committee recently were provided with a revised protocol for *An Observation Study to Evaluate Measures of Quality of Obstetric Care (APEX)*. The revised version incorporates a sample size based on a clustered observational study design. The strategy of this design is predicated on the assumption that patients within the same hospital (cluster) tend to be more similar than patients from other hospitals and, therefore, it is more efficient to limit the size of the cluster and maximize the number of clusters.

Thus, to obtain the overall sample size of about 120,000 eligible deliveries, each MFMU center's sample size will be based on the anticipated average annual number of deliveries occurring at its affiliated hospitals. The plan is for twenty five hospitals to participate in the study. The data will be collected over a three-year period, helping NICHD's fiscal crunch by spreading the capitation costs out over a longer period of time. The NICHD budget situation also has caused a postponement of the scheduled start-up of the study from January to March of 2008.

However, the pilot study is still planned to be conducted this fall. The proposed strategy is for each hospital to collect data over a two-week period at the same rate as the full study. Like the main study, the BCC will randomly assign the days on which patients are to be enrolled. Data from the pilot study will be analyzed to assess whether they adequately measure quality of care. If not, changes will be made before the main study begins.

Initial training for the APEX study will take place on October 10, prior to the next Steering Committee meeting. The pilot is scheduled to take place between November 26 and December 9, 2007, provided that at least two thirds of the participating hospitals have IRB approval. All pilot data must be entered (using the new web data entry system) by December 21.

Hospitals and staff will become certified by participating in the pilot study. Hospitals that are not ready in time to participate in the official pilot will be required to collect data in a similar fashion for two weeks and key it for certification purposes before they start the main study. This can take place any time from January 1 through February 29, 2008.

CAPPS Enrollment on Target to End

The month of August proved to be the highest recruiting month for the CAPPS trial in 2007, with 214 patients randomized for a total of 9,284 women. At this rate, recruitment of the 10,000 patients needed for the sample size is predicted to finish by the end of this year. Approximately 2,400 women will be enrolled to the observational Prediction study when the RCT reaches its sample size.

The protocol subcommittee is in the process of deciding which analytes in the observational study will be investigated to better understand the etiology of preeclampsia and for their potential to predict the development of preeclampsia. Ideas have been solicited from other members of the Network and these, along with the subcommittee suggestions, will be prioritized during the October Steering Committee meeting.

GDM Trial to Finish in November

After five years, randomization is nearly complete in the GDM trial which has a total sample size of 950 gestational diabetic patients. Accordingly, deadlines for screening and randomization have been set: November 2nd will be the last day for an OGTT test and November 16 is the last day for enrollment or randomization (including Group III). It is expected that the results of this trial will be reported at SMFM's annual meeting in 2009.

Cost Cap Reinstated for Ancillary Studies

Prior to 2000, while Dr. Donald McNellis was the NICHD Project Scientist for the MFMU Network, a policy was established whereby ancillary studies were limited to a cost of \$50,000. By definition, an ancillary study is an observational study which supplements an ongoing Network protocol, and the study population is either identical to, or a subset of, the patients enrolled in the main study.

Given the worsening constraints on the NICHD budget, Dr. Spong has decided to reinstate this cap on the cost of ancillary studies. As a result of this policy, she hopes that when investigators finalize a study protocol for implementation, they will incorporate up-front the critical objectives and outcomes that can be achieved through the research objectives and procedures. Of course, investigators also are encouraged to explore other resources to finance additional protocol-related research.



MFMU Protocol Prioritization (by Susan Pagliaro)

It's that time again! With the impending start of APEX, the centers' PIs and NCs will be asked after the October Steering Committee meeting to review the trials and studies in the queue to recommend the next one to be implemented. For the prioritization process, each center assigns a score based on scientific and clinical importance, potential impact, and cost effectiveness and feasibility within the Network. The protocols receiving the top scores are provided to the Prioritization Committee which recommends the next study for implementation based on scientific merit, funding and feasibility.

The protocols that are in the queue include:

Cord Gas Values and Neurodevelopment – Drs. Thorp (UNC) and Blackwell (UTH)

The primary aim of this observational study is to determine how often neonatal encephalopathy and abnormal neurodevelopment at age two occur in a cohort of term and near term infants born with and without metabolic acidemia.

Evaluation of a “Rescue” Approach to Antenatal Dosing of Corticosteroids – Dr. Wapner (Columbia)

The aim of this trial is to determine the efficacy of a rescue course of corticosteroids for patients who have received a previous course of steroids more than seven days previously and are at high risk for preterm delivery under 32 weeks.

Periviable Preterm Birth Study – Dr. Mercer (CWRU)

The primary objective of this study is to determine the epidemiologic characteristics of periviable birth at 20-26⁶ weeks gestation, with attention to antecedent and proximate causes, clinical course according to individual cause, and clinical risk factors specific to periviable birth.

A Randomized, Placebo-Controlled Trial of Vitamins C and E Supplementation to Prevent Recurrent Preterm Premature Rupture of the Membranes – Dr. Sciscione (Columbia)

This randomized controlled trial aims to determine if dietary supplementation with vitamins C and E in women with a previous history of pPROM will decrease the risk of pPROM in a subsequent pregnancy.

A Randomized Study Comparing Vaginal Progesterone and 17- alpha hydroxyprogesterone caproate (17-OHPC) in the Prevention of Preterm Birth – Drs. Caritis and Simhan (Magee)

The hypothesis of this trial is that treatment with weekly IM injections of 17 alpha-hydroxyprogesterone caproate reduces the risk of preterm birth in women with a prior preterm birth to a greater degree than does daily intravaginal progesterone.

The STAN Trial: A Randomized Clinical Trial of Fetal ECG ST Segment and T wave Analysis as an Adjunct to Electronic Fetal Heart Rate Monitoring - Drs. Belfort & Varner (Utah), Saade & Hankins (UTMB)

This randomized trial of fetal STAN, an adjunct to conventional electronic fetal heart rate monitoring, will evaluate if STAN decreases the risk of fetal compromise (a composite adverse neonatal outcome defined as one or more of the following outcomes: intrapartum fetal death, neonatal death, Apgar score ≤ 3 at 5 minutes, seizure(s), cord artery pH ≤ 7.05 and BD ≤ -12 , presence of neonatal encephalopathy).

Tocolysis for Preterm Labor with Intact Membranes – Dr. Mercer (CWRU)

The hypothesis for this trial is that acute tocolysis with magnesium sulfate for women suffering preterm labor at 24 – 33,6 weeks of gestation will not reduce infant morbidity and mortality.

Volunteers Sought to Help with SCAN Neonatal Data Forms

With the exception of one center and a few ancillary sites, all of the Network centers now are participating in the SCAN trial. As a result, 662 women have been screened and 23 patients randomized as of September 12th.

Neonatal and NICU forms are being revised since it was recognized that some of the data points commonly collected on neonates are no longer being used or have been updated. Also a survey of centers confirmed that some of the procedures formerly done in the NICU are now being done in the newborn nursery. A few volunteers are needed to help review the modified forms and the relevant sections in the manual. If you have relevant NICU experience and would like to help, please

e-mail Sharon Gilbert (sgilbert@biostat.bsc.gwu.edu) to volunteer.

At the last MFMU Network Steering Committee meeting it was decided that centers no longer need to submit the qualifying ultrasounds of randomized patients for central review. This is to simulate a real-world situation where scans are not usually subjected to multiple reviews. As a result, the certification process will be more rigorous. Therefore, sonographers should review the manual and training slides and follow instructions very carefully when preparing their certification scans. The de-identified certification scans are to be submitted to the BCC which will forward them on for central review.

SCAN Trial Needed Despite New Findings

The August 2 issue of the *New England Journal of Medicine* published the results of a British study on progesterone and the risk of preterm birth among women with a short cervix. The investigators, Dr. Eduardo Fonseca et al concluded that progesterone treatment of women with a short cervix reduced the rate of early preterm delivery in this research trial. The Network's subcommittee for the SCAN trial reviewed the design and other details of this study and have decided that the study differed significantly from the Network's SCAN trial and concluded that SCAN should continue with no changes. The three main reasons -- differences in study population, timing and study drug -- are described below.

First, the British study included women who were at high risk of preterm delivery for other reasons (eg, twin gestation and prior preterm delivery), while the SCAN trial

randomizes only nulliparous women. Second, the British study only included women whose cervix measured 1.5 cm or less at 20-25 weeks. This cervical length was found in only 1.7% of the population at this gestational age. The SCAN trial differs in approach in that patients are recruited at an earlier gestational age (16-22 weeks gestation), with a cervical length of less than 3cm. Thus approximately 10% of the nulliparous population is being exposed to a longer period of potentially protective treatment.

Finally, a different type of progesterone (micronized progesterone administered as a vaginal suppository) was used in the British trial. The type of progesterone being used in the SCAN trial (17 alpha-hydroxyprogesterone caproate -17OHP) has been shown in another Network trial (Meis et al, NEFM, 2003) to be effective in reducing preterm delivery in a high-risk population.

People in the News



Three months ago, **Lenny Wambugu** joined the MFMU software programming staff at the BCC to pursue a career in information systems, his major at the University of Maryland. He is working with the other staff to develop the new website data entry system for the APEX study, in addition to supporting the current FOXPRO software used for current data forms. Lenny was born in

Kenya, but spent a number of years in the U.S. while his parents attended college here. He enjoys playing tennis, travel, independent movies and music, and will begin graduate school at GWU studying information technology next spring.

MFM Investigator Recognized as Innovator

Kjersti Aagaard-Tillery, M.D., Ph.D., who until recently was a Network investigator at the University of Utah and is now at Baylor College of Medicine, was recognized by NIH Director, Dr. Elias Zerhouni, at the NIH Director's Pioneer Awards and NIH Director's New Innovator Awards program on September 19. According to Dr. Zerhouni, the NIH is "making a major investment in the future of science with five-year grants totaling more than \$105 million to 41 exceptionally innovative investigators, many of whom are in the early stages of their careers."

This is the first year that the NIH New Innovator Awards, which are reserved for new investigators who have not received NIH regular R01 research or similar grants, were given and the fourth time the Pioneer Awards have been issued. Both programs are part of the NIH Roadmap for Medical Research initiative that tests new approaches to supporting research. With her award, Kjersti will continue her studies initiated at the University of Utah and the Oregon National Primate Research Center focusing on how maternal obesity programs genetic modifications and adaptations in the developing fetus that predispose it to adult diseases, such as diabetes.

NIH selected the award recipients through a special application and application process. More than 260 experts from the scientific community identified the top individuals from over 2200 competitive grant proposal applicants, with the NIH Director's Advisory Committee performing the final review and recommending the recipients to Dr. Zerhouni. Twelve individuals were selected for the Pioneer Award and each will receive \$2.5 million in direct costs over five years. The twenty-nine recipients of the New Innovator Award each will receive \$1.5 million over five years. Information about the 2007 New Innovator Award is available at http://grants.nih.gov/grants/new_investigators/innovative_award/index.htm. More information on the Pioneer Award is at <http://nihroadmap.nih.gov/pioneer>.

SMFM Abstract Selection Announced

For the second year in a row, the results of *two* MFMU Network trials will be presented in the Opening Plenary session at the 2008 SMFM annual meeting. An additional Network abstract was selected for one of the oral sessions and nine were chosen as posters. One abstract was not accepted. The orals will be presented for feedback at both the October and January Steering Committee meetings, and the posters at the January meeting. Following are the selected orals:

- #1 Plenary **Dwight Rouse, MD, A Randomized Controlled Trial of Magnesium Sulfate for the Prevention of Cerebral Palsy**
- #3 Plenary **Margaret Harper, MD, Randomized Control Trial of Omega-3 Fatty Acid Supplementation for Recurrent Preterm Birth Prevention**
- Oral Session **Alan Tita, MD The MFMU Cesarean Registry: Impact of Gestational Age at Elective Repeat Cesarean on Neonatal Outcomes**

Out of a field of 1047 abstracts submitted to the Scientific Program Committee for review, eighty six were singled out as oral presentations, including eight for the main plenary session, and 660 were accepted as posters. The Program Committee consists of 98 general reviewers and 27 senior reviewers. Each abstract was initially critiqued and ranked by four reviewers; those on the borderline were assessed further by the senior reviewers.



Volunteers Needed for Manuscript Reviews

The Network's Publications Committee holds bi-weekly conference calls to discuss policy and procedures, the status of pending manuscripts and to review manuscript drafts. Last year the Network published a record 21 manuscripts in leading medical journals. Each of these manuscripts underwent a rigorous review process prior its submission to a journal. The MFMU web site contains a "page" where manuscripts are posted, written comments are input by the reviewers, and revised versions are uploaded by the investigator.

Thanks to the many Network investigators who have reviewed papers! More volunteers are needed to peer-review manuscripts and, subsequently, be available for the Publications Committee's final review of the paper. Six

manuscripts have been reviewed since July, with several more in the pipeline.

Network members are also invited to participate in the scheduled Publication Committee calls, which are all held at 11:00 AM Eastern Time. Generally, the calls are held on the second and fourth Friday of each month, but the schedule is subject to change depending on holidays and meetings.

Following are the dates of the calls for the rest of this year: October 5, October 19, November 2, November 30, December 7 and December 21. These dates and the manuscripts slated for review are also listed on the MFMU website calendar. Please contact Susan Pagliaro, MFMU Network Coordinator, if you have questions or want to volunteer as a reviewer.



MFMU CALENDAR

Steering Committee Meetings

July 12 – 13, 2007
October 11 – 12, 2007
January 10 – 11, 2008
April 10 – 11, 2008
July 10 – 11, 2008
October 23 – 24, 2008

Professional Meetings

January 28 – February 2, 2008, SMFM
Annual Meeting, Dallas
March 26, 2008 – March 29, 2008, SGI
Annual Meeting, San Diego

On the Light Side

*First with correct answer to June's Brain Teaser:
Russ Miller, Columbia*

September's Brain Teaser

Joe, a buyer for a certain government department, was instructed to purchase a certain commodity for \$20,000. After making a diligent search, he found a seller who offered three different grades of the item, each at a certain price. Joe placed the order, buying some of each grade. His order was such that the number of items he bought in each grade was equal to the unit price in dollars. For example, if the unit price in one of the grades were \$50, he bought 50 of those. And he spent exactly \$20,000.



What is the smallest total number of items he could have bought?

*The first to get the correct answer will receive special recognition.
Please submit to: Lucy_L@biostat.bsc.gwu.edu.*