General Clinical Research Center

Volume 10, Issue 1

Summer 2003

GCRC NEWS

INSIDE THIS ISSUE:

FROM THE DIRECTOR

The "dog days" of summer have brought not only vacations, but some unsettling news about congressional budget allocations for the NIH in general and the National Center for Research Resources (NCRR) that supports GCRCs. The GCRC Program Directors' Association will be joining other biomedical research societies to encourage Senators to vote next month for Dianne Feinstein's (D-CA) 1.3 billion dollar add-on amendment to bolster NIH funding, but the outlook is problematic at best. If the amendment fails to garner the requisite 60 votes, Plan B will be to work on members of the House and Senate subcommittees who will be responsible for hammering out the final NIH budget this fall.

Also this fall some of the leadership of the National GCRC Program Directors' Association will be meeting with Dr. Elias Zerhouni, Director of the NIH, to exchange ideas about re-engineering clinical research in the US and the role of GCRCs in that process. A synopsis of that meeting will be a topic for a future newsletter.

This current issue represents a departure from previous newsletters. Due mostly to the combination of old age and writer's block, I have turned over much of the task of highlighting the Center to those who actually are responsible for its resources and success. Information is provided by Barbara Frentzen, our Research Subject Advocate, Doug Theriaque and Jon Shuster, who oversee the Data Services Laboratory and biostatistical activities and George Henderson, who directs the Core Laboratory. Our new Nurse Manager, Teresa d'Angelo, puts in an important plug for doing industry sponsored trials in the GCRC. Also in this newsletter is a synopsis of the upcoming eighth annual Science of Clinical Research course run by the GCRC and open on a first-come, first-serve basis to trainees and faculty at the Health Science Center who are interested in careers in clinical investigation. This is also the first required course (with graduate-level credit) for fellows of the Advanced Post-Graduate Program in Clinical Investigation (APPCI), funded by the University's K-30 grant.

Future issues of the GCRC Newsletter will highlight both additional Center resources and some of our many outstanding scientific protocols, including a biosketch and friendly gossip about the investigators. Happy reading!

Research Subject Advocate

By Barbara Frentzen, ARNP (frentzen@gcrc.ufl.edu)

The NIH's National Center for Research Resources (NCRR) established the new position of Research Subject Advocate (RSA) in the GCRCs in response to troubling deaths of volunteers enrolled in research studies at some of America's prestigious research universities.

The Research Subject Advocate in the GCRC is available to help investigators and research staff increase their knowledge about regulatory responsibilities, and implement processes that will improve the safety of research subjects.

The job of the RSA, as with any new role, is flexible and differs somewhat at the 82 GCRCs throughout the US. One principal goal, however, is to help educate faculty, trainees and support staff about:

- Current guidelines with respect to patient safety
- Good Clinical Practice (GCP)
- Adverse event reporting
- Data and safety monitoring
- Clinical Laboratory Improvement Act
- HIPAA
- Conflict of Interest

Another goal of the RSA program is to help investigators develop a prospective plan to monitor the data and safety of the subjects enrolled in their studies. This Data and Safety Monitoring Plan is required for conducting a study on the GCRC. The RSA is also responsible for ensuring that the monitoring plan, approved by both the IRB and the GCRC Advisory Committee (GAC), is fully implemented and that the protocol carried out on the GCRC complies with the IRB- and GAC-approved protocol.

The RSA helps investigators report adverse events promptly to the appropriate agencies. The RSA can help research subjects directly by

- Determining that they understand the study in which they are participating
- Providing education about clinical research in general
- Serving as an objective witness to the consent process or an evaluator of a subject's understanding of the study purpose, procedures, right to withdraw, etc.
- Serving as an advocate in case of a misunderstanding
- Receiving, discussing, and resolving questions, concerns or complaints
- Resolving issues related to medical bills that a subject may have received inappropriately. (Adapted from Kraybill and Zeldin, UNC.)

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The RSA for the University of Florida

General Clinical Research Center (GCRC) is

Barbara Frentzen, ARNP

352-265-0680, extension 4-3715

frentzen@gcrc.ufl.edu

Research Subject Advocate (cont)

The RSA for the University of Florida GCRC is Barbara Frentzen. She is a nurse practitioner and has worked in clinical research for 18 years. She administered the University of Florida Institutional Review Boards (Gainesville Health Science Center, Jacksonville Health Science Center, and campus) from 1995 to 1998 and has expertise in the protection of human subjects.

Barbara is available Monday through Friday from 8 a.m. to 4 p.m. Her office is located in the GCRC, Room 3202. Her telephone number is 352-265-0680, extension 4-3715. Her email address is frentzen@gcrc.ufl.edu. If you have a question about research in general, about an issue related to your specific study, or about research regulation, she will be happy to discuss it with you. You can contact her whether or not you have a study currently ongoing in the GCRC.

Safety of research subjects is a concern for all of us—both research personnel and the public. While the responsibility for the safety of subjects ultimately belongs to the Principal Investigator (PI) of a research study, independent monitors and Data and Safety Monitoring Boards can assist the PI.

For more information about data and safety monitoring, contact Barbara.

RSA

Barbara Frentzen, ARNP

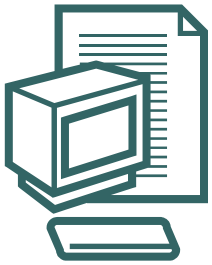
GCRC, Room 3202

352-265-0680

extension 4-3715

GCRC Resource Focus: Data Services Laboratory by Doug Theriaque, M.S. (theriaqu@gcrc.ufl.edu)

The Data Services Laboratory resides within the GCRC (3rd floor of STH, room 3207) and is supported by a total of 3.25 FTE. The GCRC Biostatistician, Dr. Jon Shuster (0.75 FTE), works in conjunction with the DSL staff in its statistical activities and is responsible for its overall direction. He is also responsible for the review of all protocols submitted to the GCRC Advisory Committee and for the GCRC's statistical education programs.



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GCRC Resource Focus: Data Services Laboratory (cont)

The Informatics Core Director, Douglas Theriaque (1.0 FTE), oversees the day-to-day activities of the DSL, including user orientation and education, system security, installation and administration of hardware and software, and the development of Web-based data systems. Mrs. Cindy Wang, M.S. provides programming support as a 1.0 FTE Coordinator of Computer Applications and Mr. Saurav Chandra rounds out our staff by providing 0.50 FTE computer support.

The DSL is the central location for planning and implementing all biostatistical and informatics research activities on the GCRC. Our mission is to ensure the statistical quality and data integrity of all GCRC protocols and to provide complete computing support for all GCRC investigators and staff. These undertakings are accomplished through:

- Review of all protocols with outside statistical support prior to submission to the GCRC Advisory Committee
- Consultation during planning and all other stages of a protocol execution. Areas typically addressed include study design, power analyses, randomization plans and data analyses.
- Data management consultation. Software recommendations and/or development; facilitation of data entry, access, and storage; and addressing security issues are commonly discussed.
- Computing support. Principal Investigators and their staff are allowed access to and provided support for a wide range of computing resources including Web and Email access, productivity (MS Office), statistical and power (SAS, Prophet, nQuery), nutritional (Nutritional Data Systems, ProNutra), and database software (MySQL).

For a complete list of DSL resources, point your browser to: http://www.gcrc.ufl.edu/computing.html.

In summary, the DSL provides a wide variety of services to support your project from its inception through completion. Before submitting your next GCRC protocol, be sure to meet with Jon (jshuster@gcrc.ufl.edu) and Doug (theriaqu@gcrc.ufl.edu) to review your needs and develop a well-rounded plan that will ensure the success of your project.

For a complete list of DSL resources, point your browser to:

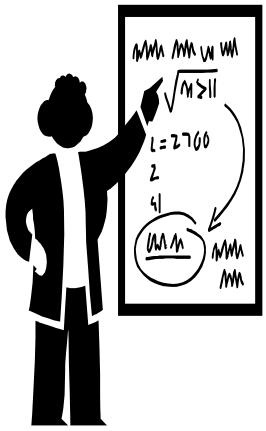
www.gcrc.ufl.edu/computing.html.

DSL on the Web!
www.gcrc.ufl.edu/computing.html

Biostatistical Corner 1.0

P-values

by Jonathan J. Shuster, Ph.D.
(jshuster@gcrc.ufl.edu)



This is the first in a series of biostatistics articles for the GCRC Newsletter. Since all researchers must deal with "P-values", whether in their own research, or in reading the work of others, it would be a good idea to start here for our first article. The following reference will begin our discussion. This was a double blind, placebo controlled trial.

Robbins GK, Addo MM, Troung H, Rathod A, Habeeb K, Davis B, Heller H, Basgoz N, Walker BD, Rosenberg ES. Augmentation of HIV-1-specific T helper cell responses in chronic HIV-1 infection by therapeutic immunization. AIDS. 2003 May 23;17 (8):1121-6.

"The augmentation of HIV-1-specific T helper cell responses was achieved in five out of five vaccine recipients and none out of four controls (P = 0.008, Fisher's exact test)."

The P-value asks the question: What is the probability of seeing results as extreme or more extreme than that observed, under the presumption that the populations from which the data were obtained were equivalent? (i.e. in this case, that the vaccine was useless.)

Note that a P-value applies to one specific experimental question.

Fisher's Exact Test works as follows: Suppose we have two players and nine cards with five labeled "Response" and four labeled "No Response". Randomly assign 5 cards to player "Vaccine" and the other 4 to Player "Placebo". [If the vaccine is truly useless, then the fate of each patient can be viewed as predestined, with the labels (vaccine or placebo) really assigned in exactly this fashion.] What is the probability that we observe a result at least as extreme as the actual (i.e. Vaccine gets all five "Response" cards.) You can try this at home repeatedly dealing from a deck of 5 Spades (Response) and 4 Hearts (No Response). But the mathematical answer to this is 0.0079 (i.e. P=0.008).

Healthy skeptic questions: (a) Was this the primary endpoint of the study, as documented in the protocol? After the fact, there might be dozens of ways to compare the treatments with respect to efficacy. The investigators need to hang their hat on a specific outcome, declared in the protocol document. [They could,

(Continued on page 6)

jshuster@gcrc.ufl.edu
294-0004
PO Box J200212

BIOSTATISTICAL CORNER 1.0 P-VALUES (CONT)

using Multivariate Methods, declare a specific collection of outcomes in the

protocol document. Note that if they declare multiple endpoints, there is an increased burden of proof on each one, over the evidence required by a single endpoint.] (b) They actually assigned 10 patients (5 vaccine and 5 placebo). One placebo patient was unevaluable for a lack of baseline measures, rendering response assessment impossible. Was this the planned number, or was this a result of an interim analysis on the way to a larger sample size? The paper does not clarify this, but the authors should have documented the study design as to actual and target patient accrual.

Red Flag #1: If we flip a balanced coin 100 times, there is a 30% chance that at some point in the sequence the proportion of heads will differ significantly from 0.5 at P<.05. [There would be 100 P-values obtained along the way.] This certainly raises a concern about the lack of documentation of the planned sample size in the above abstract.

Red Flag #2: If we had four truly equivalent treatments (A,B,C,D) and we randomly assigned 50 patients to each (as planned) and did a single analysis of study at the end, there is a 20% chance that at least one pair would be significantly different at P<.05 (two-sided), using as a yardstick, an absolute T-value of 1.96 or higher. To ensure protection against a spurious association, it would take a T-value of 2.57 (individual P-value of 1.0%) to declare significance. The probability that the largest (in absolute value) of the T-values associated with the six pairwise treatment comparisons exceeds 2.57 , when indeed all treatments are truly equivalent, is 5%. In actuality, six tests are being run (#1:A vs. B,#2: A vs. C, #3: A vs. D, #4: B vs. C, #5: B vs. D, and , #6: C vs. D).

Because of this increased burden, a 4-treatment study seeking the best treatment (with 80% power at a studywise P=.05) needs about 50% more patients **per treatment arm** (3 times as many total patients) as a 2-treatment study.

Red Flag #3: If we are correlating one collection of variables (say 5) against another set of variables (say 10), we would be conducting 50 correlation analyses (10 of the second variable for each of five of the first). You would be most unlucky, if you did not find at least one significant at the P<.05 level. This kind of exploratory analysis can be reported, as long as we fully disclose what was analyzed. If one looks at the data, even in an informal way, and selects out what appear to be significant associations, and then asks the statistician to confirm these impressions, selection bias will result.

In summary, either in your own research or in evaluating the research of others, ask this truth in advertising question: "Is the P-value telling you what it claims?"

Healthy skeptic question:

Was this the primary endpoint of the study, as documented in the protocol?

GCRC Core Laboratories

By George N. Henderson, PhD, Director (hendegn@medicine.ufl.edu)

Courtesy of the Rockefeller Archive Center

GCRC Core Laboratories include Sample Processing Laboratory (contact Dorothy Macharaga, 4-4970, macharag@gcrc.ufl.edu), Biomedical Mass Spectrometry Laboratory (contact Minghong Jia, Ph.D., 392-4529, jiam@gcrc.ufl.edu) and DNA Bank (contact Tomy Mathew, 4-4970, methewt@gcrc.ufl.edu). The Sample Processing Lab processes, barcodes, provides short-term storage of samples, and performs routine laboratory analyses for glucose, lactate, β-HCG and urinalysis. The DNA bank is currently being set up and will be operational in about two months. It will store serum, plasma and DNA from patients and will become a unique repository for genetic investigations. In this Newsletter we highlight the Mass Spectrometry Laboratory.

Biomedical Mass Spectrometry (BMS) Laboratory

Overall direction of this and other core laboratory facilities is provided by George Henderson. Day-to-day management of the Lab is provided by Minghong Jia, an expert biological mass spectrometrist who was recruited from Case Western Reserve University about 18 months ago. Last December, we hired Azeem Hasan, an expert protein mass spectrometrist from Cleveland Clinic Foundation.

The BMS laboratory is equipped with state-of-the art MS instruments, including LC-MS/MS (2 instruments with electro- and nano-spray and APCI interfaces), CE-MS/MS, GC-MS/MS (2 each), 2D-nano HPLC and 2D proteomic systems, capable of performing both identification and quantification analyses involving large and small biomolecules. Request for additional instrumentation is pending. The major analytical services and technical expertise that the Lab can provide include:

1. Method development and structural determination with modern mass spectrometry in conjunction with chromatographic and other separation technologies for analysis of xenobiotics (drugs, metabolites) and natural occurring small molecules (neuro and other peptides, biomarkers, nucleic acids, lipids, aminoacids and large biomolecules, such as proteins, in complex biological fluids and tissues.
2. Proteomics, including 2D gel, 2D HPLC and nanospray LC/MS for probing and mapping protein molecules, including determining sequence, posttranslational modification, quantitative and functional proteomics.
3. Separation and purification of trace level target analytes, including uses of gel chromatography and electrophoresis.

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GCRC Core Laboratories (cont)

Courtesy of the Rockefeller Archive Center

4. Educational and training opportunities involving basic and applied analytical technologies, with emphases on mass spectrometry and chromatography methodologies for biomedical studies.

In summary, the BMS Laboratory provides project-based biomedical mass spectrometry method development and analysis, and technical support for GCRC and other biomedical research. We would be happy to assist you in the development of your project. Our Laboratory has the capability to analyze virtually any molecule of biological or biomedical significance. The organic BMS laboratory is located in room M2-236, Medical Sciences Building. Please contact Dr. George N. Henderson (392-6193; 392-2321, hendegn@gcrc.ufl.edu) or Dr. Minghong Jia (392-4529, jiam@gcrc.ufl.edu) for MS analytical support, project development or technical consultation.

Bionutrition & the GCRC by Meena Shankar MS, RD

(shankarm@gcrc.ufl.edu)

The GCRC Bionutrition Core is staffed by a Research Dietitian and five Metabolic Cooks trained to measure and prepare specialized diets. The Research Dietitian and Metabolic Kitchen staff provide a number of services to investigators. The Research Dietitian can assist in developing or reviewing nutrition protocols. This includes assessment of each protocol's nutritional needs, completion of a literature review and development of appropriate diet methodology.

The Bionutrition staff can meet protocol requirements with specialized diets, nutrient intake data collection and anthropometrics. The Research Dietitian can develop and implement tools for assessment of dietary intake including the use of food frequency questionnaires, diet history forms and food records. Nutrient controlled meals can be prepared for inpatient and outpatient research studies involving adult and pediatric subjects.

Other services include: patient assessment, education, utilization of two nutrient data analysis software programs and reassessment to ensure compliance to research protocols. The staff has also developed methods to maximize palatability of nutrient controlled study formulas. Currently, several nutrition protocols are in progress or have recently concluded.

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BIONUTRITION & THE GCRC (CONT)

Studies in progress include an outpatient study that is evaluating the effects of a regular diet vs. gluten free casein free diet on severity of symptoms in autistic patients. This study has required pre-packed outpatient meals prepared by the Metabolic Kitchen staff and extensive review of diet records.

The GCRC also has two investigators examining differences in learning impairment, biochemical/hormonal parameters and functional MRIs in patients with early onset morbid obesity and Prader-Willi syndrome. Other nutrition related studies include medication studies involving patients with cystic fibrosis, pancreatitis, congenital lactic acidosis and kinetic studies in healthy controls.

A recently completed outpatient study assessed the impact of vitamin B6 deficiency on homocysteine metabolism. This study required five weeks of low vitamin B6 meals for each subject.

The GCRC will soon have a metabolic cart that will be available for use in GCRC sponsored protocols. GCRC staff members will be trained to perform indirect calorimetry measurements. By utilizing the GCRC Research Dietitian and Research Nurses, investigators will be able to study energy expenditure in nutritionally at risk populations in an inpatient and outpatient setting.

For more information, please contact Meena Shankar MS, RD at 265-0680 ext 43713.

Parvo TrueOne 2400 Metabolic Cart

PHARMACEUTICAL INDUSTRY SPONSORED TRIALS

BY TERESA D'ANGELO, RN, BSN (danget@shands.ufl.edu)

Did you know that the resources of the GCRC are available to investigators conducting Phase 1-4 clinical trials sponsored by the pharmaceutical industry? The GCRC has 6 inpatient beds and 4 inpatient/outpatient beds along with 4 outpatient visit rooms. Capabilities available in the GCRC include administration of investigational drugs, specimen collection and processing, pharmacokinetic sampling, monitoring of vital signs and obtaining EKGs. A metabolic cart and a fully stocked procedure room are available for use by investigators. In addition, a metabolic kitchen with a full dietary staff, including a Registered Dietician, is on site. An Investigational Pharmacist works with the GCRC to ensure compliance with investigational drug storage requirements. The Research Patient Advocate and the GCRC administrative and nursing staff are available to investigators to help navigate regulatory and administrative issues. The GCRC is THE place to conduct your next pharmaceutical industry sponsored trial! Please contact Ann Coutu at 265-8909 to discuss how the GCRC can help you.

The GCRC is THE place to conduct a pharmaceutical industry sponsored trial!

GCRC Summer Internship Program

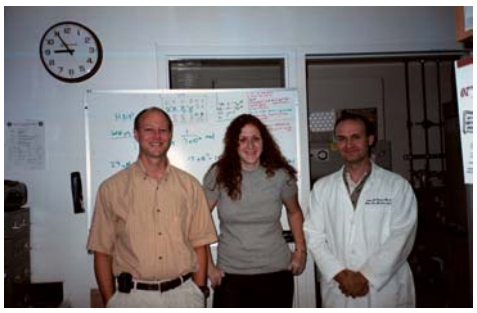
By Peter Stacpoole, Ph.D., MD, Director, GCRC

Dr. Peter Stacpoole, Carlos Rosello, Andrew Hsia, Jennifer Srygley, Jennifer Rehm, Michelle McGarry, Nina Singh, Randall Martin
Not Pictured—Jewel Greywoode

Each summer several students undertake a 10-week elective rotation on the GCRC to engage in clinical investigations with faculty mentors. Students choose from among ongoing inpatient, outpatient and scatterbed protocols that provide a high level of patient and mentor contact during the summer months. As part of their elective, students round on the GCRC inpatient service and attend a weekly luncheon meeting interacting with GCRC investigators, review their individual progress and present synopses of their projects. At the completion of their rotation, they submit a written review of the scientific basis of their project and of their own contributions to it.

Jennifer Rehm, Dr. Desmond Schatz, Michelle McGarry

Margaret Francis, ARNPand Randall Martin



Dr. Terry Spencer, Jennifer Srygley, Quenton Rance

Dr. Ammon Peck and Michelle McGarry

EIGHTH ANNUAL SCIENCE OF CLINICAL RESEARCH (SCR) COURSE (ROOM C1-3, COMMUNICORE BUILDING, 2:00— 5:00 PM)

Session	Topic (Discussion Leader)	Date
1	**Course Introduction – Challenges and Opportunities for the for the Physician-Scientist (Peter W. Stacpoole)** • Goals and Overview of Course – Peter Stacpoole • Integration with UF's Advanced Postgraduate Program in Clinical Investigation–Marian Limacher • GCRC-based Research and Awards – Mark Brantly • GCRC Advisory Committee – Larry Edwards • BREAK • Perspective of a College Dean – C. Craig Tisher • Perspective of a Junior Investigator – Terry Spencer • Description of Student Project – Ron Marks	**Mon. 9/29**
2	**Grants and Grantsmanship, Part I – Where the Money Is and How to Keep It (Frederick Southwick)** • Structure and Function of NIH – Kirsten Madsen • BREAK • Writing a Competitive Grant – Fred Southwick • Understanding the Grant Review Process – Fred Southwick	**Tues. 9/30**
3	**Epidemiology Methods, Part I – (Nabih Asal)** • Overview of Study Designs • Cross-sectional and Ecological Studies • Case-control Studies • BREAK • Cohort Studies	**Wed. 10/1**
4	**Epidemiology Methods, Part II – (Nabih Asal)** • Diagnostic Accuracy • BREAK • Causality	**Thurs. 10/2**
5	**Study Design and Analysis in Patient-oriented Research, Part I – Clinical Trials (Jon Shuster)** • Types of Trials and Protocol Development – Jon Shuster • Blinding and Placebos – Jon Shuster • Study Design – Jon Shuster • BREAK • Randomization – Jon Shuster • Sample Size/Power – Jon Shuster	**Fri. 10/3**

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EIGHTH ANNUAL SCIENCE OF CLINICAL RESEARCH (SCR) COURSE (ROOM C1-3, COMMUNICORE BUILDING, 2:00— 5:00 PM) (CONT)

Session	Topic (Discussion Leader)	Date
6	**Statistical Methods in Data Analysis in Patient-Oriented Research (POR) (Ron Marks)** • Overview of Statistical Methods –Ron Marks • Intention to Treat vs. Per Protocol –Ron Marks • Multiple Significance Testing – Ron Marks • BREAK • Introduction of Web-based Research Approach to Clinical Trials–Ron Marks • Meta Analysis –Ron Marks	**Mon 10/6**
7	**Grants and Grantsmanship, Part II (Peter Stacpoole)** • Alternatives to NIH – Nancy Schaefer • Finding Private Funding – Jennifer Binegar • BREAK • Intellectual Property and Confidentiality – Richard Melker • Conflicts of Interest and Ethics in Medical Research – Richard Melker	**Tues 10/7**
8	**Federal Guidelines and Scientific Integrity in POR – Rules to Know Up Front (Peter Iafrate)** • IRBs and Informed Consent – Peter Iafrate • Data and Safety Monitoring for Clinical Trials – Barbara Frentzen • BREAK • "Ownership" of Human Tissues and Fluids – Barbara Frentzen • HIPAA – Barbara Frentzen • FDA Governance of New Product Development – Susan Beltz	**Weds. 10/8**
9	**Special Topics in POR – Biotechnology and Student POR Proposals (Peter Stacpoole)** • Biotechnology – William Farmerie • Pharmacogenetics – Julie Johnson • BREAK • Critique of Student POR Proposals – Nabih Asal, Mark Brantly, Ron Marks, and Peter Stacpoole	**Thurs. 10/9**
10	**Grants and Grantsmanship Redux – Student POR Proposals (Peter Stacpoole)** • Critique of Student POR Proposals – Peter Stacpoole, Ron Marks, Nabih Asal, and Mark Brantly	**Fri. 10/10**

NOTE: For Jacksonville staff, the teleconference will be held in the Deal Board Room.