New Leadership at ICTR Clinical Trials Networks

Effective July 1, Patrick McBride, MD, MPH, professor of Medicine and Family Medicine, has assumed the chair of the Wisconsin Network for Health Research (WiNHR) Advisory Committee, as well as a UW leadership role with the Midwest Area Research Consortium for Health (MARCH).

McBride will forge strong relations with MARCH Clinical and Translational Science Award (CTSA) partners and work towards creating an effective multi-site network for clinical investigators, a network of networks.

Most recently the UW SMPH Associate Dean for Students, McBride brings years of research, teaching, and leadership experience to the WiNHR position. His primary research focus is the management of lipid disorders and the quality of cardiovascular disease prevention in clinical practice and communities. He is currently an investigator on several NIH grants, including a clinical trial of the effects of smoking cessation on patient outcomes.

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Utilizing Diverse Clinical Research Networks for Cardiovascular Patient Trials

Although influenza infection is known to be associated with increased risk of cardiovascular events and data suggests vaccination might attenuate cardiac risk in high-risk populations, influenza vaccine is widely underutilized in this population. More recently, various trials have suggested that higher-dose influenza vaccine may overcome impaired immune responses in those with advanced heart disease and provide a cardio protective benefit.

Orly Vardeny, PharmD, MS, associate professor of Pharmacy (SOP) and Medicine (SMPH), is planning a large multi-center, randomized clinical trial to test the cardio-protective effects of high- versus standard-dose influenza vaccine in high-risk cardiovascular patients. Titled: INVESTED (INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure), Vardeny developed the trial with ongoing assistance from WiNHR and the multistate Midwest Area Research Consortium for Health (MARCH). If approved by the NIH, the proposed trial will enroll 9300 participants over three influenza seasons. The WiNHR and MARCH sites are expected to contribute 1800 of the 9300 subjects.

Vardeny is also currently in negotiation with Novartis Pharmaceuticals to conduct another trial to evaluate the effect of Entresto, a dual-acting angiotensin receptor-neprilysin inhibitor, on endothelial function in patients with heart failure. Again, WiNHR and MARCH are providing assistance with trial budgets, sponsor negotiation, multi-site recruitment plans, and coordinating local research services. If approved, UW-Madison will serve as the IRB of record for the new Novartis trial.

Patrick McBride, MD, MPH, professor of Medicine and Family Medicine and incoming WiNHR Advisory Committee Chair, comments, “We are enthusiastic about the possibility of testing a new agent utilizing a unique mechanism of action for a medical problem of such vital importance to our population.”
**The Marshfield Report**

*By Robert Steiner, MD, Executive Director, MCRF\nICTR Associate Executive Director*

It is with great pleasure that I announce that Marshfield Clinic was granted Full Accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Accreditation became effective December 2014 after a two year review process, and the initial accreditation period will last three years. Research participants at Marshfield Clinic can be reassured knowing that our research integrity program meets high level, objective standards for the quality and level of protection for clinical studies.

Benefits to the organization include respect from peer institutions, a competitive edge with research sponsors looking for sites, a reduced risk of non-compliance stemming from having comprehensive and meaningful policies and procedures, and an ongoing commitment to continuous quality improvement of our research programs. Heartfelt congratulations are due to Linda Jaros, Marshfield Clinic research compliance officer, and her team for this tremendous achievement.

I have a long personal connection with human subject protection and IRBs. My own career in human subject research dates back to the early 1990s, and I have continuously conducted clinical research since then. Between 2000 and 2010, I was an Institutional Review Board (IRB) member at Oregon Health & Science University (OHSU), and I served on the OHSU IRB Chair Advisory Council for several years. At Marshfield Clinic, I am the institutional official with overall oversight of our IRB and Human Subject Protection Program.

Nationwide, this is a busy time for IRBs and for professionals involved in human subject protection. My accompanying feature (back cover) outlines upcoming changes in the manner in which informed consent is obtained in this country. I encourage investigators to keep abreast of these developments and to submit comments where requested, if you have concerns about specific draft guidance being issued by federal agencies.

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**UW Announces Post Approval Monitoring Program**

*(Adapted from UW-Madison Graduate School announcement, April 2015)*

The UW-Madison Office of the Vice Chancellor for Research & Graduate Education has launched a Post-Approval Monitoring (PAM) Program to provide increased education and guidance for researchers who have received Institutional Review Board (IRB) approval. The PAM Program offers researchers guidance and best practices to implement their IRB-approved research in ways that protect research participants, ensure the ethical conduct of research, and validate the reliability of research results.

The PAM Program facilitates research by ensuring it is implemented in a manner consistent with the approved protocol and applicable policies and regulations. To that end, IRB-approved studies may be selected for post approval monitoring. During a monitoring visit, a post-approval monitor will review how research is being conducted, and provide researchers with helpful feedback and tools for self-evaluation of research practices. More information on how research will be selected for monitoring and other useful resources can be found online kb.wisc.edu/gsadminkb/page.php?id=46261.

Rebecca Marnocha, PharmD, associate executive director for the ICTR Clinical Research Infrastructure System and the ICTR Clinical and Translational Research core, notes, “Post approval monitoring programs are not unique to UW-Madison; they are an expectation of all human research protection programs. Increasingly, formal PAM programs are a...”

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Marc K Drezner, MD, ICTR executive director and SMPH senior associate dean for clinical and translational research, comments, "Pat has a long and productive history of statewide cardiovascular prevention research. His career experiences have prepared him well to understand the challenges of conducting statewide and multi-site clinical research and to take a leadership role in our ICTR research networks that support clinical and translational research throughout the state of Wisconsin and beyond."

McBride adds, "I am honored and enthusiastic to assume a leadership role with ICTR, an organization that is the embodiment of the Wisconsin Idea, and which can improve the health of the population."

**New Administrative Director**

In addition, Jennifer Bufford, MS, CCRC, CCRP, is the new ICTR administrative director of both the WiNHR and MARCH research networks, replacing Debra Kruser. In this capacity she will develop collaborative research partnerships and facilitate multi-center clinical and translational research studies throughout Wisconsin and the Midwest.

Bufford has a broad range of translational and clinical research experience including work as a clinical research coordinator, a research compliance educator, and a Medicare Coverage Analyst. Most recently, she was a global team manager with the University of Arkansas for Medical Sciences CTSA program. In that position, she was responsible for managing the biomedical informatics and translational technologies programs, assisting faculty in their research endeavors, tracking and evaluating their institute’s overall progress towards meeting goals and objectives, and playing an active role in obtaining continued funding.

Drezner notes, "Both the WiNHR and MARCH networks were well served by Howard Bailey and Debra Kruser, who worked tirelessly to build research infrastructure for statewide and multi-state trials. We wish them well in their new endeavors."

"McBride and Bufford bring both experiences and fresh perspectives to our support for multi-site research," he continues. "WiNHR has experienced substantial growth in supported projects over the past five years. ICTR has been extremely fortunate to recruit such high caliber leadership for our ongoing efforts to complement the experienced staff already in place."

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**What is the Wisconsin Network for Health Research?**

Established in 2005, WiNHR is a partnership of the UW SMPH, Marshfield Clinic Research Foundation, Aurora Health Care, and Gundersen Health System. WiNHR was established to promote statewide research and to assist in moving research results from bench to bedside, by allowing investigators to perform clinical, translational, comparative effectiveness and health outcomes research across a variety of platforms. WiNHR also collaborates with sponsors to find optimal sites, patient populations; and investigators to achieve meaningful research outcomes and maximize the value of research dollars.

More information about WiNHR partner sites and supported projects can be found on the newly redesigned WiNHR pages on the ICTR Web portal (ictr.wisc.edu/WiNHR). To discuss potential projects, please contact Jennifer Bufford, bufford2@wisc.edu, (608)262-7217.

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**What is the Midwest Area Research Consortium for Health (MARCH)?**

Six NIH Clinical and Translational Science Award (CTSA) sites united to form the Midwest Area Research Consortium for Health (MARCH) in 2012 to promote multi-site clinical and collaborative research across the upper Midwest.

Member sites include Indiana University, Mayo Clinic, Medical College of Wisconsin, The Ohio State University, University of Minnesota, and University of Wisconsin.

Like WiNHR, MARCH provides infrastructure necessary to improve efficiency and effectiveness of regional clinical research by minimizing duplication, standardizing data capture and reporting, and enhancing multi-site study performance through best practice methodologies.

The central offices of MARCH are housed in UW SMPH, with administrative support provided by ICTR. More information can be found on the MARCH web site (www.marchhealth.org/) and local investigators can discuss questions and potential projects with Jennifer Bufford, bufford2@wisc.edu, (608)262-7217.
The Assay Services group at the Wisconsin National Primate Research Center (WNPRC) is one of the laboratories affiliated with UW ICTR in the collaborative model used by the ICTR Translational Technologies and Resources Core (TTRC). Assay Services provides modern, efficient, and cost-effective measurements in a centralized facility to WNPRC investigators, ICTR members, other Clinical and Translational Science Award site members, and other NPRCs, as well as to investigators at universities across the US and internationally.

Available services include method development and high throughput analyses of steroids, hormones, proteins, peptides, bioamines, biomarkers, and drug compounds to aid NIH-funded research with an emphasis on non-human and human primates.

**Multi-steroid analyses**

Custom liquid chromatography/mass spectrometry (ABSciex QTRAP) methods developed at Assay Services can measure nine different adrenal and reproductive steroids in a single injection. This approach is readily adaptable to measure steroids in blood, urine, and cerebral spinal fluid, as well as live tissue secretions and hair.

A prerequisite for the approach was the ability to measure steroids with very high sensitivity. For instance, the level of quantitation for estrone and estradiol is 2.4, 1.2 pg/ml, respectively and this is well below physiological levels for both men and women. This sensitivity allows performance of special projects that require measurement of small amounts of sample containing low concentrations of analyte.

**Vitamin D metabolites**

Another important focus of QTRAP LC/MS/MS has been the development and quantitation of the Vitamin D metabolites including 25-hydroxyvitamin D2&3 and 1,25-dihydroxyvitamin D2&3. Methods originating at Assay Services have allowed measurements of very low concentrations of Vitamin D in samples from both human and nonhuman primates; the limits of detection are 0.5 ng/ml and 15 pg/ml for 25-hydroxyvitamin D and 1,25-hydroxyvitamin D, respectively.

Ziegler comments, “Our lab participates in the National Institute of Standards and Technology (NIST) quality assurance program for Vitamin D measurement. The high quality of these assays has contributed to both publications and extramural research support for several ICTR investigators."

Development of still newer assays for Vitamin D metabolites, in particular, a panel including 24,25- dihydroxyvitamin D2&3, 25-hydroxyvitamin D, 1,25- hydroxyvitamin D, cholecalciferol (Vitamin D3), and ergocalciferol (Vitamin D2), will contribute to understanding individual variation in human metabolism of the Vitamin D hormone and identify the individual metabolic pathways for Vitamin D.

**High through-put studies**

Assay Services has modified many analyses for high throughput-studies. The QTRAP LC/MS/MS has multiplexing capabilities so that twice as many samples can be run within a given time frame allowing mass spectrometry methods to be more practical. Radioimmunoassay methods for proteins, peptides and steroids allow hundreds of samples to be run in a single assay. Additionally, the service can analyze high volumes of samples, when required for a large study.

**Voucher funding available**

Assay Services is one of the laboratories participating in the ICTR Voucher Awards program offered through TTRC (ictr.wisc.edu/FundingOpportunities). Craig Atwood, PhD, associate professor of medicine and an ICTR voucher recipient comments, “The voucher award from ICTR allowed us to use Assay Services to generate preliminary data important for our ongoing applications for grant funding. In addition, the data acquired have helped us refine our experimental protocols for steroid measurements and complimented other data collected for our project.”

More information can be found on the Assay Services home page (wprcfs.primate.wisc.edu/assay/assay.php), or by contacting Toni Ziegler, ziegler@primate.wisc.edu. For service, please submit an online consult form (ictr.wisc.edu/hormonelab).

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**Meet Amita Kapoor: Assay Services Methodology Researcher**

Amita Kapoor joined Assay Services in September 2011. She completed her bachelor’s degree in Biology and Psychology at the University of Toronto in 2002. Amita earned her PhD in physiology at the University of Toronto in 2008, and completed postdoctoral fellowships at the University of Toronto and the Harlow Primate Laboratory at UW. Her research focus is on non-invasive measures to assess the relationship between hormone exposure during pregnancy and subsequent maternal hormone levels and behaviors during the postnatal period. In Assay Services, Amita specializes in developing novel methodology for QTRAP mass spectrometry including detection of multisteroids in human and nonhuman primate hair. She can be contacted at akapoor@primate.wisc.edu.
Case Study 1: Longitudinal Study of Aging Biomarkers

Biomarkers are a mainstay of aging studies such as the Midlife in the US project (MIDUS), a national, longitudinal study of health and well-being based at UW-Madison. Led by Carol Ryff, PhD, professor of psychology and director of the UW Institute on Aging, the project is tracking behavioral, psychological, social, and biological aging of US residents between ages 25 and 85. Currently, participants are being evaluated during an overnight stay in hospital units including the ICTR Clinical Research Unit (CRU). This second longitudinal visit is five years after the initial assessment and is designed to capture age-related changes. UW ICTR is one of three centers that facilitate this project, which has been ongoing for over a decade.

The clinical visit includes collection of biological specimens (blood, urine, and saliva) which are used for many different hematological, endocrine, and immune tests. The ICTR Assay Services unit has played a key role in providing high-throughput and high quality assays for the salivary and urine specimens. Specific tests include the levels of cortisol and alpha amylase in saliva, to monitor stress-related physiologic changes. In addition, the Assay Services unit employs sophisticated electrical chemical detection methods to quantify the excretion of catecholamine neurotransmitters into urine, providing an indirect index of the activity of participant’s autonomic nervous system. These biomarkers are then correlated with other demographic and psychosocial information about each individual to better understand how societal and personal factors affect health and the aging process.

Christopher Coe, PhD, professor of psychology and MIDUS assay core leader, states, “The importance of the contributions of the ICTR Assay Services unit cannot be overstated. They are essential and have enabled MIDUS to be a sustained success.” Coe continues, “Equally valuable are the contributions of the nurses and staff at the CRU who are involved in the overnight hospital stays.”

The MIDUS study is funded by the National Institute of Aging and has generated over 600 scientific publications. More information about MIDUS can be found at www.midus.wisc.edu.

Case Study 2: Continually Improving Vitamin D Assays

Research on Vitamin D has a long history on the UW Madison campus, beginning early in the twentieth century and continuing through today. As the clinical ramifications of Vitamin D insufficiency are increasingly understood to extend beyond bone health to diverse conditions possibly including cancer, cardiovascular disease, asthma, and cognitive impairment, intensive research has focused on identifying appropriate diagnostic measures and treatment regimens. UW ICTR has played a strong role in recent years in supporting Vitamin D-focused investigations and development of novel methods.

Assay Services has worked with several ICTR investigators to develop highly sensitive measures for Vitamin D metabolites in both clinical populations and primate surrogates. In collaboration with Neil Binkley, MD, professor of Medicine, and Curtis Hedman, PhD, Wisconsin State Laboratory of Hygiene, the laboratory group developed tandem mass spectrometry measures of 25-hydroxyvitamin D2&3 and 1,25-dihydroxyvitamin D2&3 that allowed multi-species primate comparisons.

These assays were also used in a recent study led by Karen Hansen, MD, professor of Medicine, investigating the effects of proton pump inhibitors (PPIs) on osteoporotic fracture risk. In addition to performing Vitamin D metabolite assays, Assay Services researchers developed an HPLC method to measure the PPI omeprazole for this study.

Karen Hansen
MD

Hansen comments, “I am delighted to work with Toni Ziegler at the Assay Laboratory. Over the past decade, the lab has analyzed human samples for several of my research trials. One prime example of their excellent service was measurement of serum omeprazole levels.”

She continues, “I found two methods papers describing how to measure omeprazole in serum, but only one laboratory in the country would perform the assay, at a cost of $500 per sample. Toni was able to use the methods papers to develop the assay, and subsequently measured serum omeprazole levels in all of my study participants with reliable results and more cost-effectively. This was in addition to their highly sensitive measurements of Vitamin D metabolites.”

Finally, Assay Services researchers have extended their collaboration with Binkley to construct and validate a Vitamin D metabolite panel to measure biochemical pathway intermediates in individuals. This panel is thoroughly validated, matches the Mayo Clinic method and Assay Services is currently assaying the first ICTR project human samples for Binkley and colleagues.

Read more online (ictr.wisc.edu/NewsletterExtra).
Federal Agencies Issue Draft Guidance on Multiple Human Subject Research Topics

(A discussion by Robert Steiner, MD, Executive Director, MCRF)

Pending national level initiatives may introduce substantial changes to the protection of human subjects in research in this country. First, the Food and Drug Administration (FDA) has issued Draft Guidance for Industry, Clinical Investigators, and Institutional Review Boards for Use of an Electronic Informed Consent in Clinical Investigations.

This draft guidance provides recommendations for clinical investigators, sponsors, and IRBs on the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations of medical products. The guidance on electronic consent adds to the toolkit of the clinical and translational researcher by offering the opportunity to broaden the mechanisms to obtain informed consent.

Second, the NIH has announced a Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. NIH published a request for public comments in the NIH Guide for Grants and Contracts in December 2014. Deferral to a single IRB is intended to increase the efficiency of research review and establish other changes in research approval processes needed for multi-site and multi-institutional studies. The UW has taken a leadership role in creating an IRB reliance (IRB rely) for the 62 CTSA sites across the country, which promises to enhance the efficiency and quality of multi-site clinical research in the U.S.

Third, the DHHS Office of Human Research Protections (OHRP) recently issued Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care. OHRP is specifically addressing what risks to subjects are presented by research that evaluates or compares risks associated with standards of care, and which of these risks are reasonably foreseeable and should be disclosed to prospective research subjects as part of their informed consent. This guidance is likely to have been in response to the controversial SUPPORT study of oxygenation in neonates.

OHRP determined in March 2013 “that the informed consent document for this trial failed to adequately inform parents” of what risks their babies might face via study enrollment. Although OHRP ultimately suspended its non-compliance actions against the University of Alabama, the draft guidance has been issued and is the subject of current debate.

Finally, the recently passed law, Newborn Screening (NBS) Saves Lives Reauthorization Act of 2014 includes text in section 12 stipulating that all research involving newborn screening blood spots will require informed consent. This statute will change the process by which research involving de-identified blood spots is performed, by adding the requirement for explicit parental consent.

As these examples indicate, federal regulation of research continues to evolve. Researchers have a responsibility to stay abreast of proposed, as well as actual, changes and provide their informed opinion as appropriate.

Read more about these issues online (ictr.wisc.edu/newsletterExtra).

Post Approval Monitoring... Continued from page 2

condition of accreditation and multi-site research participation. More importantly, they are pivotal to the sustainability of any clinical and translational research enterprise by assuring research compliance, identifying educational and process improvement opportunities, and enhancing subject safety. “

Dan Uhlrich, UW associate vice chancellor for research policy adds, “Historically UW-Madison has relied on school-, departmental-, center-, or study team-based monitoring. The PAM Program infuses much needed personnel effort into these activities. This enhances our ability to track compliance issues and trends across the entire campus infrastructure, and enables a focus on preventative solutions, such as training and guidance tools.”

Uhlrich continues, “Research teams can also reach out to the PAM group during research development to proactively seek guidance on complicated study conduct issues – to me that is the good news.”

Keep UW ICTR up-to-date with NIH

Acknowledging ICTR Support

Publications arising from UW ICTR supported research should acknowledge support by stating “Supported by grant UL1TR000427 from the National Center for Advancing Translational Sciences, NIH.”

Don’t Forget PubMed Central Submissions

Investigators holding an NIH grant, or receiving services through an organization like the NIH-funded ICTR, must submit publications arising from such support to the NIH PubMed Central Public Access site (publicaccess.nih.gov/). Failure to comply can lead to sanctions from NIH, including withdrawal of grant support.

Many campus resources are available to assist investigators (ebling.library.wisc.edu/help/nih.php), and individual assistance can be obtained by contacting Ebling Library staff, nihpolicy@library.wisc.edu.