Message from the Executive Director

The Duke Clinical Research Institute is dedicated to making a meaningful difference in the lives of patients and their families. This newsletter highlights some of the means by which we are able to produce important and innovative research. First, we would like to acknowledge the key help of investigators around the globe who facilitate our work. Our valued site investigators and their teams bring a passion for excellence and an amazing spirit of collaboration to each project. Representing this passion, we feature one of our collaborators at Black Hills Cardiovascular Research in Rapid City, South Dakota. The Black Hills team has been an enthusiastic partner in research, consistently generating high-volume enrollment activity across a number of trials.

Second, we are announcing the extension of a partnership with our important academic research collaborators at the Canadian VIGOUR Centre (CVC) to include “Duke West” (otherwise known as Stanford). Our triumvirate agreement will facilitate innovative evidenced-based research and broader educational collaborations. Special thanks to Paul Armstrong, MD, director of the CVC, for hosting myself and others from DCRI this past spring to finalize the details of this agreement.

Finally, risk-based monitoring has become a new buzzword in the clinical trials industry. In this edition, you can read how DCRI has been a leader in utilizing risk-based monitoring in every large trial since GUSTO-1 in 1990.

Thanks once again for your continued help with our mission.

Eric D. Peterson, MD, MPH, FAHA, FACC
Executive Director,
Duke Clinical Research Institute
Professor of Medicine, Cardiology
Fred Cobb Distinguished Professor of Medicine

SITE SPOTLIGHT

Black Hills Cardiovascular Research, Rapid City, South Dakota

We asked Roger DeRaad, MN, CNP, director of Black Hills Cardiovascular Research to describe the collaborative relationship between his site and the DCRI.

Tell us about your site.
Black Hills Cardiovascular Research is the clinical research department of Regional Heart Doctors—14 cardiologists who provide specialty cardiovascular services to a large geographic area, including western South Dakota and a population of approximately 350,000. This area also includes 2 veterans affairs (VA) hospitals, a central VA clinic, and several American Indian reservations, and it comes with numerous challenges of rural health care.

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SITE SPOTLIGHT

Black Hills Cardiovascular Research
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How long have you worked with the DCRI and how did the relationship start?
We began conducting research around 16 years ago (1998), starting with a National Institutes of Health (NIH) study called PEACE. Over a 2-year period, we added a couple more studies and received an invitation from the DCRI to consider participating in the phase-III VALIANT trial.

The DCRI team performed a “site selection visit” and although they noted that we were totally inexperienced, they also saw that we had a good practice setting to develop clinical research potential. The staff at the DCRI encouraged us to participate. Throughout the trial, the mentoring they provided was probably more important than the monitoring they conducted. We were ultimately successful with the VALIANT trial and learned in the experience that clinical research takes a dedicated focus. Our collaboration with the DCRI has continued now for 16 years.

What is it like working with the DCRI compared with your experience working with other academic or clinical research organizations / sponsor operations teams?
After 16 years and more than 200 trials, working with many research organizations, the DCRI is still our favorite organization to work with.

OPERATIONS INNOVATION & EFFICIENCY

(NOT SO) RISKY BUSINESS
The DCRI leads the way with risk-based monitoring of its clinical trials

Monitoring is a significant part of clinical trials, but there is often little science to drive individual trial-monitoring plans. The DCRI, however, has found a way to leverage existing data into an effective monitoring strategy. Monitoring refers to the methods used by sponsors and clinical research organizations (CROs) to oversee the conduct of and reporting of data from clinical trials. This oversight includes communication with the investigators and study site staff; review of the study site’s processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor.

When my staff attempt to qualify what is different about working with the DCRI, the most common descriptor they use is “personal.” Instead of being “just a site number in someone’s database,” the staff at the DCRI have consistently treated us as colleagues with a common mission.

What differentiates a DCRI study?
We preferentially participate in trials being conducted by the DCRI because we know that a significant amount of time has been spent trying to develop a practical protocol that works well for the clinicians and study staff. When we began conducting research around 16 years ago (1998), starting with a National Institutes of Health (NIH) study called PEACE. Over a 2-year period, we added a couple more studies and received an invitation from the DCRI to consider participating in the phase-III VALIANT trial.

The DCRI team performed a “site selection visit” and although they noted that we were totally inexperienced, they also saw that we had a good practice setting to develop clinical research potential. The staff at the DCRI encouraged us to participate. Throughout the trial, the mentoring they provided was probably more important than the monitoring they conducted. We were ultimately successful with the VALIANT trial and learned in the experience that clinical research takes a dedicated focus. Our collaboration with the DCRI has continued now for 16 years.

What lessons have been learned as a result of the collaboration?
Our collaboration with the DCRI on protocols and projects brought us together with successful sites that willingly shared their experiences, operating procedures, and best practices with us as we grew and matured. My staff continue to benefit now as they share their own experiences and best practices with others.

What did your team bring to the relationship that enhanced the experience for the DCRI?
We feel that support from the DCRI leadership and staff tipped the scales for us as we considered establishing a clinical research infrastructure. We have since grown from a staff of 1 to 15, and although we still struggle with the issues common to all research sites, we are proud of our accomplishments.

We hope that DCRI staff feel they have also benefited from our long association, and we would strongly encourage the DCRI to continue to identify, encourage, and support other cardiovascular practices that are interested in developing a research infrastructure.
OPERATIONS INNOVATION & EFFICIENCY

(NOT SO) RISKY BUSINESS
Continued from page 2

Effective monitoring of clinical investigations by sponsors is critical to the protection of human subjects and the conduct of high-quality studies. However, the sheer size and scope of many clinical trials make in-person inspections of every site and complete verification of every piece of data impractical. For that reason, many sponsors and CROs are now turning to risk-based monitoring.

“This has always been our standard approach on the international mega trials managed by the DCRI, but more recently it has been incorporated into smaller phase-II and phase-III trials.”

John Alexander, MD, MHS
Director of Cardiovascular Research at the DCRI

This approach, which is based on draft guidelines released by the U.S. Food and Drug Administration, incorporates centralized monitoring practices to ensure the quality of clinical trial data. The DCRI has been a leader in this field, utilizing risk-based monitoring in every large trial since GUSTO-1 in 1990.

“This has always been our standard approach on the international mega trials managed by the DCRI, but more recently it has been incorporated into smaller phase-II and phase-III trials,” said John Alexander, MD, MHS, director of cardiovascular research at the DCRI.

Studies have found that risk-based monitoring is actually more likely than routine visits to clinical sites and full data verification to ensure subject protection and overall study quality. A recent review of onsite monitoring findings collected during a multicenter international trial determined that centralized monitoring activities could have identified more than 90 percent of the findings identified during onsite monitoring visits.

Risk-based monitoring is important because it does not monitor everything equally but rather monitors things that are truly important to trial safety and efficiency, Alexander said.

“We should only be monitoring when there is risk to things we care about: the protection of human subjects and the integrity of the data that will be used to make important decisions,” said Alexander.

EXPLORING COLLABORATION OPPORTUNITIES

Connecting with academic partners within North America

The DCRI has a long history of collaborative projects with academic partners, both nationally and internationally. This spring, the DCRI expanded its collaborative relationship with the Canadian VIGOUR Centre (CVC) to include Stanford University, taking advantage of long-time working relationships with Kenneth Mahaffey, MD, and Robert Harrington, MD, former DCRI faculty.

This collaboration offers thought leadership in the architecture, design, management, and analysis of novel clinical trials, related protocols, and substudies.

Advantages of this collaboration include the unique opportunity to inform and guide industry and regulatory health agencies, potentially impact health policy, and direct future research and funding to unmet and/or emerging health needs. In addition, this North American academic research organization (ARO) would provide the infrastructure to:

- Demonstrate enhanced return on clinical trial research investments by creating opportunities to collectively explore related registries and databanks that serve to cost-effectively translate knowledge into improved patient care and outcomes
- Adhere to the highest bioethical conduct standards in the course of striving for improved health in the global community
- Encourage strong academic thought leadership focused on improving patient care and health care systems through knowledge translation
- Explore mechanistic insights from research performed
- Perform relevant quality assurance and health care economic studies
- Develop ARO–physician-led operations teams that are aware of and responsive to the changing clinical trial landscape
- Produce timely, peer-reviewed publications
**BETTER TREATMENT OPTIONS**

**Interferon-free regimen provides viable, less toxic treatment option for HCV patients**

**Regimen of ledipasvir and sofosbuvir provides high rates of sustained virologic response in all treatment groups**

Although knowledge and treatment options regarding the hepatitis C virus (HCV) have improved drastically over the last few years, the current standard treatment of interferon alfa and weight-based ribavirin can cause a variety of unwanted side effects.

A recent study has found that a regimen of ledipasvir and sofosbuvir provides an effective treatment for patients with HCV genotype one with less toxicity. This multicenter, randomized, phase-III study treated patients for 12 or 24 weeks with or without the use of ribavirin. The results showed that despite whether the patients’ treatment regimen included ribavirin, all treatment groups had rates of sustained virologic response (an efficacy measure for HCV that looks for the absence of the RNA HCV virus in blood serum) that exceeded 97 percent.

The study results were published in the May 15 edition of the *New England Journal of Medicine* and included contributions from the DCRI’s Andrew Muir, MD, MHS (pictured left). In this trial, rates of response were generally uniform, irrespective of baseline patient characteristics. In patients with cirrhosis, which has traditionally been difficult to treat with interferon-based therapy, there appeared to be no marked effect on rates of response and the safety profile. However, the study was not specifically designed or powered to formally compare response rates in patients with or without cirrhosis, so these results need to be further tested. The results further suggested that regimens adding ribavirin or extending treatment to 12 weeks do not result in better response rates than a regimen of 8 weeks of ledipasvir-sofosbuvir. This could mean a shorter treatment regimen would be equally effective. The groups receiving ledipasvir-sofosbuvir plus ribavirin experienced side effects such as fatigue, insomnia, cough, pruritus, and anemia.

**PROJECT MILESTONES**

Congratulations to the TRANSLATE-ACS Outcomes team! The database was locked on May 31.

Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) is a prospective, observational, longitudinal study that will evaluate the real-world effectiveness and use of adenosine diphosphate (ADP) receptor inhibitor therapies among patients with myocardial infarction treated with percutaneous coronary intervention during index hospitalization.

This study is sponsored by Eli Lilly and Daiichi Sankyo, Inc. Principal investigators are Tracy Wang, MD, MHS, MS, and Eric Peterson, MD, MPH.

Kudos to the team for this tremendous effort!

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**Cool facts**

- **Enrolled 12,365** patients at **233** sites from April 2010 to October 2012
- **Obtained 19,504** bills with more than **230,000** bill charge records
- **Call center conducted 47,801** phone interviews
- ** Analyzed medical records for more than 6,592** events for adjudication
RECRUITING STUDIES

CAT-HF
Cardiovascular Improvements with Minute Ventilation-targeted ASV Therapy in Heart Failure

The study objective is to evaluate minute ventilation (MV)-targeted adaptive servo-ventilation (ASV) in addition to optimized medical therapy (OMT) versus OMT alone at 6 months in patients with acute decompensated heart failure. The study is a randomized, unblinded, multicenter trial with parallel group design. Subjects are randomized to either control (OMT for chronic heart failure) or active treatment (OMT plus use of MV-targeted ASV) in a 1:1 ratio. Up to 215 subjects overall will be randomized, and recruitment is underway.

ClinicalTrials.gov Identifier: NCT01953874
Sponsor ResMed
Learn More about Participating Lisa Hatch, Project Leader 919.668.7516 lisa.hatch@duke.edu

DUR001-106
A Phase 1, Open Label, Single Dose Study To Investigate The Pharmacokinetics, Safety and Tolerability Of Dalbavancin In Hospitalized Children Aged 3 Months to 11 Years Receiving Standard Intravenous Anti-Inf ective Treatment For Bacterial Infections

This phase-I study is investigating the pharmacokinetics, safety, and tolerability of a single dose of intravenous dalbavancin in hospitalized pediatric patients aged 3 months to 11 years (inclusive) with known or suspected bacterial infection. The anticipated enrollment is 36 patients.

ClinicalTrials.gov Identifier: NCT01946568
Sponsor Durata Therapeutics, Inc.
Learn More about Participating Jennifer Murphy, Project Leader 919.668.8795 jennifer.murphy@duke.edu

HARMONEE
Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNeich’s Combo StEnt

This single-blind study is assessing a novel drug-eluting stent platform for percutaneous coronary revascularization in patients from the United States and Japan with ischemic coronary disease and non–ST-segment elevation myocardial infarction acute coronary syndrome. Patients will be randomized 1:1 to receive the Combo Dual Therapy Stent as the investigational treatment arm or a Xience everolimus-eluting stent as the active-control arm. It is expected to include up to 50 sites in Japan and the United States with an anticipated enrollment of 572 subjects.

ClinicalTrials.gov Identifier: NCT02073565
Sponsor OrbusNeich Medical
Learn More about Participating Allison Handler, Senior Project Leader 919.668.8885 allison.handler@duke.edu

HFN-FIGHT
A randomized, double-blinded, placebo-controlled study where placebo or a glucagon-like peptide (GLP)-1 agonist (liraglutide 1.8 mg) will be administered daily by subcutaneous injection, initiated at discharge and administered for 6 months.

This study tests the hypothesis that, compared with placebo, therapy with a subcutaneous GLP-1 agonist after the acute heart failure syndrome discharge period will be associated with greater clinical stability at 6 months as assessed by a composite clinical endpoint. The anticipated enrollment is 300 patients.

ClinicalTrials.gov Identifier: NCT01800968
Sponsor DCRI
Funded by National Heart, Lung, and Blood Institute
Learn More about Participating Doris Coleman, Project Leader 919.668.8042 doris.coleman@duke.edu
### RECRUITING STUDIES

#### HFN-NEAT HFpEF
A randomized, double-blinded, placebo-controlled, crossover study to assess the effect of isosorbide mononitrate with dose up-titration on activity tolerance as assessed by (hip-worn, tri-axial) accelerometry. Approximately 100 participants will be enrolled in this 2x2 crossover study.

**ClinicalTrials.gov Identifier:** NCT02053493

**Sponsor:** DCRI

**Funded by:** National Heart, Lung, and Blood Institute

**Learn More about Participating**
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#### SPRITES
Sertraline Pediatric Registry for The Evaluation of Safety

This prospective cohort study will evaluate the risks and benefits of treatment with sertraline under real-world conditions in subjects ages 6 to 16 (inclusive) who are prescribed sertraline by a physician for up to a 3-year period and who meet all inclusion and none of the exclusion criteria for SPRITES. This study is a component of a post-approval regulatory commitment to the European Medicines Agency.

SPRITES is expected to gather meaningful information on the safety of long-term sertraline use in pediatric subjects and to evaluate the long-term impact of treatment with sertraline on aspects of cognition, emotional and physical development, and pubertal maturation. There are approximately 40 participating sites in the United States.

**ClinicalTrials.gov Identifier:** NCT01302080

**Sponsor:** Pfizer

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#### TACTICS-HF
The Targeting Acute Congestion with Tolvaptan In Congestive Heart Failure Study

This investigator-initiated, randomized, double-blinded, placebo-controlled, multicenter study is comparing the effects of oral tolvaptan versus placebo as an adjunct to a fixed dose of intravenous furosemide on dyspnea relief, renal function, and changes in clinical status in 250 patients hospitalized with acute decompensated heart failure who have a prior clinical diagnosis of heart failure and have been treated with oral loop diuretics, dose of furosemide 40 mg (or equivalent), for at least 1 month.

**ClinicalTrials.gov Identifier:** NCT01644331

**Sponsor:** Duke University through grant support from Otsuka America Pharmaceutical, Inc.

**Learn More about Participating**
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### UPCOMING EVENTS

#### ICAAC 2014
54th Interscience Conference on Antimicrobial Agents and Chemotherapy
September 5–9, 2014, Washington, DC
Walter E. Washington Convention Center
Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: systematic review of revascularization in critical limb ischemia
Jones WS, Dolor RJ, Hasselblad V, et al.
PM:24655697

The impact of a measurement and feedback intervention on blood pressure control in ambulatory cardiology practice
PM:24655694

Rationale and design of the familial hypercholesterolemia foundation Cascade Screening Panel: statement of the US Department of Health and Human Services Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
Kemper AR, Green NS, Calonge N, et al.
PM:23907646

Hyaluronan contributes to bronchiolitis obliterans syndrome and stimulates lung allograft rejection through activation of innate immunity
PM:24471427

Telavancin for hospital-acquired pneumonia: clinical response and 28-day survival
Corey GR, Kollef MH, Shorr AF, et al.
PM:24419353

Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to Staphylococcus aureus: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies
Barriere SL, Strjewski ME, Corey GR, Genter FC, Rubinstein E.
PM:24708675

Neurobehavioral functioning and survival following lung transplantation
PM:24233282

Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
Kemper AR, Green NS, Calonge N, et al.
PM:23907646

Frailty assessment in the cardiovascular care of older adults
PM:24291279

Trends in the use and outcomes of ventricular assist devices among medicare beneficiaries, 2006 through 2011
Khazanie P, Hammill BG, Patel CB, et al.
PM:24486278

Vorapaxar in acute coronary syndrome patients undergoing coronary artery bypass graft surgery: subgroup analysis from the TRACER Trial (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)
Whellan DJ, Tricoci P, Chen E, et al.
PM:24211500

Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF Trial
PM:24755148

The imperative of overcoming barriers to the conduct of large, simple trials
Eapen ZJ, Lauer MS, Temple RJ.
PM:24715072

Proportion of US adults potentially affected by the 2014 hypertension guideline
Navar-Boggan AM, Pencina MJ, Williams K, Sniderman AD, Peterson ED.
PM:24682242

Patterns and outcomes of red blood cell transfusion in patients undergoing percutaneous coronary intervention
PM:24570247

Rates of cardiopulmonary resuscitation training in the United States
Anderson ML, Cox M, Al-Khatib SM, et al.
PM:24247329

Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection
PM:24725238

Application of new cholesterol guidelines to a population-based sample
PM:24658484

Changes in the incidence of candidiasis in neonatal intensive care units
PM:24446441

Variation in congenital heart surgery costs across hospitals
Pasquale SK, Jacobs ML, He X, et al.
PM:24567024
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