The pulse of promise.
The beat of progress.
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Welcome to our 2015 annual report. Since the dawn of civilization, the creative elements of the human spirit have ensured the survival of the species. Hence adaptability has been an overarching feature of organizations “built to last” as so elegantly characterized by Jim Collins, the incisive management guru who also gave us the inspiring book Good to Great. In that book, a great organization is defined as … “one that delivers superior performance and makes a distinctive impact over a long period of time”. In his essay on the Social Sectors that addresses this subject he reminds us that, unlike the profit-driven modus operandi of a business, the vision and mission are what drives the resource engine of not-for-profit organizations such as the Canadian VIGOUR Centre housed within the University of Alberta.
CAREER DEVELOPMENT

LEADS HEARTS AND MINDS

CLINICAL-IMPACT POLICY

CONTINUOUS INNOVATION

Compass

VISION
Generate, translate and disseminate knowledge on novel diagnostic and therapeutic strategies in cardiovascular medicine acquired through collaborative research.

PROMISE
• Trusted partner
• Effective communicator
• Clinical relevance
• Scientifically robust
• Credible results
• Novel technologies
• System performance measurement
• Fulfill social contract

PURPOSE
To enhance cardiovascular health for current and future generations.

CORE VALUES
• Quality
• Collaboration
• Integrity
• Respect

OPERATIONAL PRIORITIES
• Collaborator and site retention through engagement
• Efficient project management
• Early on the ground
• Maximizing return on investment
• Linking trials/registries/populations

PURPOSE
To enhance cardiovascular health for current and future generations.
Vision, Mission, Core Values

**VISION**
Generate, translate and disseminate knowledge on novel diagnostic and therapeutic strategies in cardiovascular medicine acquired through collaborative research to enhance the health of the citizens of Alberta, Canada, and the world.

**MISSION**
Aligned with the University of Alberta and the Mazankowski Alberta Heart Institute (MAHI), our mission is to:
- Design, conduct, analyze and disseminate findings arising from novel clinical research
- Interrogate clinical trial, registry and population health data to evaluate outcomes, identify unmet needs and inform future basic and clinical research directions
- Identify, inspire and nurture the next generation of health researchers and professionals.

**CORE VALUES**
**Quality**
Aspire to the highest standard of work while respecting a balanced life perspective. Attract, mentor and retain high quality colleagues and collaborators with similar core values.

**Collaboration**
Promote and support an outstanding team that integrates a diversity of knowledge, experience, ideas, and skills supportive of our mission/vision.

**Integrity**
Perform our roles in an ethical framework which enhances our reputation an honest, trustworthy and responsible.

**Respect**
Create an innovative, engaging and inclusive work environment, appreciative of individual differences and contributions. Our workplace will be conducive to personal growth and development that is aligned with our overall mission.

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The Value Proposition of an ARO

An academic research organization (ARO) possesses scholarly values of inquiry and truth and shares knowledge in an ethical framework. Dedicated to enhancing public health, it values discovery, novel approaches and methodologies over profit. Intent upon maximizing the return on research investment, an ARO strives to exceed the operational efficiencies of a clinical research organization (CRO), and intentionally seeks funding from diverse sources beyond industry. An ARO is almost always embedded in a University and therefore reserves its right to publish its insights with objectivity. An ARO functions on a not-for-profit basis, and reinvests all sources of capital, both financial and intellectual, into the education of the next generation of health professionals, and thereby aims to fulfill its social contract to promote the public good.
As a learning organization committed to enhancing the health of current and future generations through research, CVC relentlessly pursues the generation, translation and dissemination of new knowledge addressing unmet clinical needs. This culture of learning embraces the cycle of quality that begins with health science discovery followed by its application to human disease using careful quantitative and qualitative measures. For discovery to have an impact, its efficacy must be first examined in controlled populations. Subsequently, the effectiveness needs to be evaluated through performance measures in carefully crafted patient registries acquired in selected disease states. To complete this cyclical process there must be successful dissemination of new knowledge into clinical practice resulting in meaningful differences in health outcomes at the population level. Health economic evaluation, demonstrable return on investment, and responsive health policy enrich the success and timeliness of this journey. Professional and public education are seminal components of the process occurring in parallel. The inevitable destination of this construct is a new appreciation for the unmet needs of the population and re-entry into the cycle to continue the quest for improvement in clinical and/or health system outcomes.
Our Year in Review

55
Publications that CVC’s body of research produced

124
Principal Investigators participating in CVC managed trials

196
On-site monitoring visits that occurred in Canada

136
Global users accessing CVC’s online collaborative platform

11
Industry and grant funded clinical trials underway

4,209
ECGs analyzed by CVC

900,000+
Size of data repository reflecting health of Albertans with cardiovascular disease
### Financial Summary

#### REVENUES FROM INDUSTRY-SPONSORED CLINICAL TRIALS AND EXPENSE RECOVERY

**JANUARY 1, 2015 — DECEMBER 31, 2015**

<table>
<thead>
<tr>
<th>Project</th>
<th>Sponsor(s)</th>
<th>Grant Holders</th>
<th>Term</th>
<th>Total Granted (CAD)</th>
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<tbody>
<tr>
<td>PROACT-4</td>
<td>Heart and Stroke Foundation</td>
<td>Justin Ezekowitz (PI), Padma Kaul, Robert Welsh</td>
<td>2014-2017</td>
<td>$233,000</td>
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<tr>
<td>SODIUM-HF</td>
<td>Canadian Institutes of Health Research</td>
<td>Justin Ezekowitz (PI)</td>
<td>2013-2017</td>
<td>$698,301</td>
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<tr>
<td>(ODYSSEY)</td>
<td>University Hospital Foundation</td>
<td>Justin Ezekowitz (PI)</td>
<td>2015-2017</td>
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<tr>
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<tr>
<td>Diabetes Mellitus (GDM) in Alberta</td>
<td>Canadian Institutes of Health Research</td>
<td>Padma Kaul (PI)</td>
<td>2014-2017</td>
<td>$278,139</td>
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<td>HiLo-HF</td>
<td>Heart and Stroke Foundation</td>
<td>Justin Ezekowitz (PI)</td>
<td>2015-2016</td>
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<tr>
<td></td>
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<tr>
<td>Identifying hospitalized heart failure patients who require a critical care admission</td>
<td>Heart and Stroke Foundation</td>
<td>Sean Van Diepen (PI), Justin Ezekowitz, Padma Kaul, Finlay McAlister, Cynthia Westerhout</td>
<td>2015-2016</td>
<td>$42,000</td>
</tr>
<tr>
<td>Provincial and National Costs of Unnecessary Coronary Intensive Care Unit Admissions</td>
<td>University Hospital Foundation Medical Research Competition (UHFMR)</td>
<td>Sean Van Diepen (PI), Justin Ezekowitz, Padma Kaul, Finlay McAlister, David Zygun</td>
<td>2015</td>
<td>$29,975</td>
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**“An investment in knowledge pays the best interest.”**

—BENJAMIN FRANKLIN

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### Grants

- ODYSSEY — 37%
- TECOS — 11%
- IMPROVE-IT — 7%
- GUIDE-IT — 2%
- EXSCEL — 16%
- AEGIS — 13%
- BLAST-HF — 7%
- OTHER — 7%
This study was our first effort at incorporating the opinions of patients into cardiovascular trials and warranted further investigation in broader patient populations. Interviewer-administered surveys, including rating, ranking, point-allocation and trade-off methods, such as ranking, rating, and point allocation. The methods used in this study offer a feasible approach to incorporating patient preferences into cardiovascular trials and are not limited to a single patient population.

Conclusions: Although patient preferences appear to be comparable with those of clinicians, patients may be less willing to discontinue treatment or to tolerate potential treatment complications. The methods used in this study offered a feasible approach to incorporating patient preferences into cardiovascular trials and are not limited to a single patient population.
The future of cardiovascular clinical research in North America and beyond—addressing challenges and leveraging opportunities through unique academic and grassroots collaborations

The SODIUM-HF (Study of Dietary Intervention Under 100 mmol in Heart Failure): A pilot study

Dietary sodium reduction in heart failure (HF) has been proposed and supported by multiple guidelines yet is based on limited high-quality evidence; accordingly, there is a lack of consensus amongst guidelines on the recommended level of dietary sodium intake for patients with chronic HF. Justin Ezekowt, Elosa Colen-Ramirez and their colleagues completed a pilot randomized control trial (SODIUM-HF) and found that dietary sodium reduction in HF is feasible when an individualized and structured meal plan with close follow-up is provided to patients. Additionally, an achieved sodium intake less than 1500 mg/day at 6 months of follow-up was associated with reduced BNP levels, a surrogate prognostic marker, and improved quality of life in ambulatory patients with HF on optimal medical treatment. Larger randomized control trials with clinical outcomes as primary endpoints are required to support this recommendation and confirm a better prognosis associated to lower sodium intake in patients with HF.
## Publications

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>TITLE</th>
<th>JOURNAL</th>
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“The power of accurate observation is commonly called cynicism by those who have not got it.” — GEORGE BERNARD SHAW

“Wonder is the beginning of wisdom.” — SOCRATES
“You see things; you say, ‘Why?’ But I dream things that never were; and I say ‘Why not?’

— GEORGE BERNARD SHAW

**Authors**


**Title**

The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications.

**Journal**

Can J Cardiol. 2015;31:1009-111.


**Title**

Concomitant proton-pump inhibitor use, platelet activity, and clinical outcomes in patients with acute coronary syndromes treated with prasugrel versus clopidogrel and managed without revascularization: insights from the targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes trial.

**Journal**


Patel AB, Quan H, Welsh RC, Deckert-Sookram I, Tymchak W, Sookram S, Sushitha I, Kaul P.

**Title**

Validity and utility of KCD-10 administrative health data for identifying ST- and non-ST-elevation myocardial infarction based on physician chart review.

**Journal**

CMAJ Open. 2015;3:4-13-418.

Reid R, Ezekowitz JA, Brown PA, McAlister FA, Roive BH, Braim B.

**Title**

The prognostic importance of changes in renal function during treatment for acute heart failure depends on admission renal function.

**Journal**


**Title**

The future of cardiovascular clinical research in North America and beyond - addressing challenges and leveraging opportunities through unique academic and grassroots collaborations.

**Journal**

Am J Cardiol. 2015;31:149-150.

Saranda RS, Hohlschler SH, Pfifer MA, Yuan F, Hart RG, Yusuf S, Connolly SJ, McAlister FA, Healey JS.

**Title**

Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure.

**Journal**


Sharma A, Ferguson C, Barney KR.

**Title**

Thrombocytopenia in acute coronary syndromes: etiologies and proposed management.

**Journal**

Can J Cardiol. 2015;31:809-811.

Sharma A, Khan JS, Barney KR.

**Title**

Preoperative stress tests-supersloppy investigations resulting in excessive treatment delay: a teachable moment.

**Journal**

JAMA Intern Med. 2015;175:1610-1611.

**Authors**


**Title**

Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? results from the MAGGIC meta-analysis.

**Journal**


**Title**

Incorporating patient preferences into clinical trial design results of the Opinions of Patients on Treatment Implications of New Studies (OPTIONS) project.

**Journal**


**Title**

Comparative assessment of short-term adverse events in acute heart failure with cystatin c and other estimates of renal function: results from the ASCEND-HF trial.

**Journal**

JACC Heart Fail. 2015;3:40-49.


**Title**

Diuretic response in acute heart failure: an analysis from ASCEND-HF.

**Journal**


Thanh NX, Toye I, Sau A, Kumari P, Kaul P.

**Title**

Health service use and costs associated with low birth weight: a population level analysis.

**Journal**


van Diepen S, Bakal JA, Lin M, Kaul P, McAlister FA, Ezekowitz JA.

**Title**

Variation in critical care unit admission rates and outcomes for patients with acute coronary syndromes or heart failure among high- and low-volume cardiac hospitals.

**Journal**


**Title**

Efficacy and safety of vorapaxar in Non-ST-segment elevation acute coronary syndrome patients undergoing noncardiac surgery.

**Journal**

J Am Heart Assoc. 2015;4: e002546.

van Diepen S.

**Title**

Is coronary intensive care unit volume a quality metric?

**Journal**

J Am Heart Assoc. 2015;4:e002200.


**Title**

Should dual antiplatelet therapy be used in patients following coronary artery bypass surgery? A meta-analysis of randomized controlled trials.

**Journal**


Wang X, Kinderski W, Kaul P.

**Title**

Comparison of transient associations of air pollution and AMI hospitalisation in two cities of Alberta, Canada, using a case-crossover design.

**Journal**

BMJ Open. 2015;5:e009169.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Journal</th>
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<tr>
<td>Youngson J, Ezekowitz JA, Kaul P, McAlister FA</td>
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</table>
The Pulse of Promise The Beat of Progress

Collaborative Mentoring
University of Toronto, University of Alberta, University of British Columbia

PARTICIPATING MENTORS
Shaun Goodman, Michael Yanksh, Paul Armstrong, Justin Esmail, Robert Welsh, Andrew Krahm, John Cairns, John Mancini

PARTICIPATING MENTEES
Akshay Bagai, Jay Udd, Andrew Yan, Kevin Bainey, Sean van Diepen, Mustafa Toma, Chris Fordyce

In October 2013 during the Canadian Cardiovascular Society (CCS) Annual Scientific Meeting, Dr. Shaun Goodman hosted the inaugural Collaborative Mentoring meeting supported by the Poli-Char Foundation. Present at this meeting were representatives from the University of Toronto (including the Network for Innovation and Clinical Research [NICR]), the University of Alberta (including the Canadian VIGOUR Centre), and the University of British Columbia. This meeting was comprised of senior and junior faculty cardiologists from the three universities and together they developed a set of objectives for the Collaborative Mentoring program. The objectives (which were revised in 2015) are as follows:

1. Through a forum where clinical research opportunities can be shared among faculty members, address #2-#5.
2. To introduce developing clinicians conducting clinical research (mentees) to the lessons learned from established clinician scientists/leaders (mentors) in order to enrich their career development and enhance networking opportunities.
3. To facilitate developing faculty members in establishing goals, action plans and deliverables that would enable their academic success.
4. To bring together a community of developing and established clinician scientists in order to facilitate existing or planned Canadian clinical research activities; and,
5. To establish major unmet needs in clinical cardiovascular research in Canada and capitalize on opportunities that are best realized through creative collaboration.

Following the initial meeting, five virtual meetings occurred between 2014 and 2016 together with two additional face-to-face meetings in advance of the 2014 and 2015 Canadian Cardiovascular Congress meetings. A fourth meeting is planned for October 2016.

In addition to these meetings, several of the junior faculty members are now adjudicating clinical endpoints in a large cardiovascular outcomes trial as formal members of a Clinical Endpoint Committee in collaboration with the Duke Clinical Research Institute.

In the interview featured below, Dr. Goodman discusses the objectives of the Collaborative Mentoring program in more depth:

1. Why is it important for senior clinicians to take on a mentorship role with their junior colleagues?

Mentoring provides senior clinicians with an ongoing opportunity to "give back." We’ve all been the beneficiaries of outstanding mentors who have shared their wisdom and experiences. Senior mentors helped all of us become comfortable in the academic environment, introduced us to key leaders and contacts and enhanced opportunities for networking in research areas of interest. Further, mentors have helped mentees to develop key goals and associated action plans, and provided encouragement, particularly when things (e.g., manuscripts, grant proposals, etc.) aren’t successful. Perhaps most importantly, senior mentors can serve as role models for young mentees.

2. During the collaborative mentoring sessions the junior clinicians have the opportunity to give short presentations about their area of clinical research interest. How do both the junior and senior clinicians benefit from this experience?

One unique opportunity that the mentoring meetings offer is sharing of ideas and perspectives beyond the four walls of one’s own institution or university. We’re blessed with senior mentors who are not just nationally, but also internationally recognized for their content expertise and experience in conducting clinical research. So we try to leverage this by exposing the junior clinicians to senior clinicians’ perspectives. The mentors capitalize on the enthusiasm and ideas the young researchers bring to the table which often provides fresh input and an opportunity for rejuvenation.

3. What is the role of creative collaboration at these meetings? Why is it important?

The Collaborative Mentoring initiative fosters an environment in which we can strengthen the cross-the-country relationships the Canadian VIGOUR Centre has worked hard to develop and maintain over the years while developing new ideas and engaging the "next generation" of Canadian clinical researchers. Hopefully we can work together to try and answer some important questions that aren’t always addressed by a typical industry-initiated and sponsored study.

4. One of the meeting objectives is to introduce junior faculty who are conducting clinical research to the lessons learned from established clinician scientists/leaders. What do you believe are the key lessons learned through your own experience conducting clinical research?

Persistence—there aren’t too many truly "novel" ideas but if it’s a good question, than stick with it! Don’t wander too far from the bedside—important clinical questions present themselves every day, so listen to your patients and their families! Work hard but balance your time—being productive in research, like anything in life, requires a constant juggling of priorities! Publish—we have a responsibility to the patients we engage in our research and our collaborators for all of the time and effort and trust they have placed in us to get that information out in the peer-reviewed, public domain!

5. Through your collaboration with the mentees what have you learned about their perspectives regarding the future of clinical cardiovascular research in Canada?

The future looks bright! Our mentees are excited, talented, and extremely capable individuals who simply need some protected research time, funding support, constructive criticism and positive feedback, and an occasional reminder to stay focused. If the senior mentors can offer some opportunities and guidance, there is no limit to what these mentees can accomplish.

Shaun Goodman
Trainees: The Next Generation of Health Researchers

The CVC continues its enthusiastic commitment to fostering a research environment conducive to disciplined academic inquiry and novel approaches to clinical questions and methodologies. CVC has provided research opportunities for undergraduates, medical students, and postdoctoral fellows from across Canada and from around the world. The hallmark of an academic research organization, CVC’s mission remains steadfast: to make dedicated efforts to inspire and nurture the next generation of health researchers.

In the following section, several of our young researchers discuss their research highlights and reflect upon their experience collaborating with the CVC faculty in 2015.

QENDRESA BEKA
MSc Student, Epidemiology
What would you say are your research highlights and personal achievements from 2015?
In 2015 I had the opportunity to present my research at a number of conferences and events. I presented at the Women and Children’s Health Research Institute (WCHRI) Research Day and the School of Public Health’s annual INSIGHTS event. I also had the opportunity to present results from two papers I have been working on at the 14th Symposium of the International Diabetes Epidemiology Group (IDEG). With IDEG I was awarded a travel bursary to attend the meeting and participate in a diabetes epidemiology training course.

Why did you choose to work with your mentor(s)?
I chose to work with Dr. Kaul because I was very interested in her work with gestational diabetes (GDM) and was seeking a mentor who would guide me through my program. The Master’s degree is unique because it acts as a link between course-based learning and academia. I knew I would be undergoing a steep learning curve and wanted a strong mentor to help me through the process.

What have you learned from working with your mentor(s)?
The questions I investigate are posed by my supervisor, Dr. Ezekowitz, and along the way my thinking is constantly calibrated and kept in check by our discussions. Thus I am brought up to speed—what seems an endless literature—and can contribute far sooner than I otherwise could. Dr. Ezekowitz also flags papers I may be interested in or that I would benefit from reading.

PAUL BROWN
PhD Student, Medicine
What would you say are your research highlights and personal achievements from 2015?
I presented my project on peripartum cardiomyopathy at the Mazankowski Cardiac Sciences Research Day and was awarded the Audrey Greenough-Norm Davies award for the best abstract presented by a Medical Resident. I also had the opportunity of presenting this work at Canadian Cardiovascular Congress and competed as a finalist for the Trainee Research Award.

Why did you choose to work with your mentor(s)?
I was fortunate enough to work with Dr. Armstrong as a medical student the whole year until I started my Internal Medicine residency training and wanted to shift gears in terms of research content. I was lucky enough to have Dr. Ezekowitz accept me as a trainee and support my personal and professional goals in becoming a cardiovascular clinician scientist. Dr. Ezekowitz has been a role model in every sense and has given me the foundation to develop a bright future in academic medicine.

What have you learned from working with your mentor(s)?
I was very fortunate to have worked with the VIGOUR group to publish an interesting paper associating meteorological events and decompensated heart failure using the ASCEND trial in the International Journal of Cardiology in the winter of 2014. With the help of VIGOUR I have continued working on novel and exciting research projects and have come one step closer in becoming an academic clinician scientist in Canada. Dr. Ezekowitz was also instrumental in helping me win the Sackett scholarship from the Canadian Stroke Prevention Network.

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SHARRY KAHLON
Fellow, General Internal Medicine
What would you say are your research highlights and personal achievements from 2015?
My 2015 highlights included working with a group of researchers with extensive recognition and publications. My paper on “Association between frailty and 30-day outcomes after discharge from hospital” was published in the Canadian Medical Association Journal in 2015 with the support of my research supervisors. I also presented a poster at the Society of Internal Medicine meeting.

What have you learned from working with your mentor(s)?
Dr. Ezekowitz taught me to never spread myself too thin, but to focus on the few things (both professional and personal) that excite you every time you wake up: this is the key to finding success.

DEBRAJ DAS
Resident, Internal Medicine
What would you say are your research highlights and personal achievements from 2015?
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SUMAN DHESI
Resident, Cardiology
What are some highlights from the research you have conducted in 2015?
Additionally, are there any personal achievements or awards from 2015 you would like to highlight?
I presented my project on peripartum cardiomyopathy at the Mazankowski Cardiac Sciences Research Day and was awarded the Audrey Greenough-Norm Davies award for the best abstract presented by a Medical Resident. I also had the opportunity of presenting this work at Canadian Cardiovascular Congress and competed as a finalist for the Trainee Research Award.
What have you learned from working with your mentor(s)? I have learned to always keep up a smile and be optimistic. Hard work always brings up results. There is always good in things no matter how bad they look, it is just that we have to find what we can use of it. We should never give up and that there are always better ways to do things.

JENELLE PEDERSON
MSc Student, Medicine

What would you say are your research highlights and personal achievements from 2015? My thesis examined the prognostic value of current depressive symptoms in general medical inpatients, of which one of the top-admitting diagnoses is heart failure. A major highlight was collecting data firsthand from patients and working alongside our team (supervising attendings, residents, nurses, and pharmacists) and the inpatient medical teams who supported our study—we prospectively enrolled 500 patients in just over a year. Primary data collection was a real grounding point, providing insight to patient experiences and acute care processes. In our recently published paper, we found that the presence of current depressive symptoms, but not a documented history of depression, predicted a 2-fold increased risk of short-term readmission or mortality independent of the current best risk prediction tools. This paper is a result of another major highlight, the collaboration that occurred over the last two years. From recruitment to publication, I gained invaluable support from our team and was awarded the Graduate Student Research Assistant Award as well as published the entirety of my thesis and collaborated on multiple co-authored publications, which were presented nationally and locally.

Why did you choose to work with your mentor(s)? I was introduced to Dr. McAlister by my co-supervisor, who I had worked with as an undergraduate student. The project was a great fit in terms of skills I had and would gain by training under experienced outcomes researchers-clinicians. But beyond this, it really came down to how reasonable, transparent, and respectful those initial discussions were. This was true of interactions between Dr. McAlister and me, and interactions I witnessed between my two supervisors throughout my MSc. It was also apparent early on how genuinely each privilege teaching and learning.

What have you learned from working with your mentor(s)? It is a rare opportunity to work closely with leading researchers. The mentorship provided by Dr. McAlister and my co-supervisor has been the best. Last year’s CVC annual report aptly quotes Benjamin Franklin, “Tell me and I forget; teach me and I may remember; involve me and I learn.” That’s incredibly close to how I feel about our research experiences. I was involved at each phase, from those first meetings to my own analyses and manuscript writing, and learned the research process from the ground up. Teamwork is an integral part of the research culture I experienced and it offered insight on engaging collaboration within a dynamic research team. Drs. McAlister and Rajamalar challenged my reasoning and decision-making, teaching me to focus on methodological details and always to bring it back to research questions and the big picture. I am particularly thankful for many teaching moments and their critical appraisal or “red ink.” At the same time, I felt supported and have gained a motivation to achieve my best work and pursue the highest standards.

JEYSUNDAR RADHAKRISHNAN
Postdoctoral Fellow

What would you say are your research highlights and personal achievements from 2015? Majority of my research is on maternal and neonatal outcomes of gestational diabetes using Alberta’s administrative health data. This project will build on and extend our understanding of gestational diabetes in Alberta, and provide valuable informative data for the rest of the country where this type of real-life data remains unavailable.

I am working on other cardiovascular projects too. For instance, we examined the impact of characteristics of the physician most responsible for care during a heart failure hospitalisation on mortality outcomes. The physician characteristics analysed were specialty (Cardiologist/ Internist or other), experience level, sex, country of education, and whether the physician was fee-for-service or paid through an alternative payment plan. The results showed that physician characteristics do not appear to contribute significantly to variations in patient mortality outcomes in heart failure.

Why did you choose to work with your mentor(s)? I have a background in physiotherapy, and some previous experiences in epidemiology and rehabilitation programs for patients with cardiovascular risk factors. Dr. Padma Kaul (epidemiology) and Dr. Roseanne Yuen (endocrinology) are my supervisors and Dr. Allyson Jones (physiotherapy) is my career mentor. This rare combination became possible at the University of Alberta and this completes all the gaps in my career interests. More than expected, it has been a great experience to work with these internationally recognized experts and I admire the working culture and environment at the CVC. I appreciate the learning opportunities every day and I am sure that this opportunity will make it easier to achieve my goals.

What have you learned from working with your mentor(s)? It is a great opportunity to work at the CVC. My mentors have been assisting me in every possible way. I was given opportunities to work with the team of biostatisticians to learn analytical techniques using new programs, supported in finding funding opportunities and preparing applications for grants, provided a teaching assistantship to improve my teaching skills, and given support to attend and present at conferences. Phil Jackson said “The strength of the team is each individual member and the strength of each member is the team.” This idea is realised at the Canadian VIGOUR Centre and I am so proud to be here.

NARIMAN SEPHERVAND
PhD Student, Experimental Medicine

What would you say are your research highlights and personal achievements from 2015? Like all other CVC members, I am working on research projects related to cardiovascular diseases. We studied the factors that are related to testing for natriuretic peptides in patients presenting to emergency departments (ED) with acute heart failure (AHF). The findings are now published in the Canadian Journal of Cardiology and also featured in an interview by medicalresearch.com. I presented the findings on behalf of the investigators at the 2015 Canadian Cardiovascular Congress in Toronto, ON. These findings could help AHS-Laboratory services see the health and economic effects of their initiative of expanding the access to NP testing to all emergency departments in Alberta. For regions which are planning to introduce, extend or standardize their NP testing in the ED (e.g. other provinces of Canada as well as many European countries), the results may help them recognize and address the potential target groups (e.g. care providers who are more or less likely to order the test), patients groups that should be targeted for testing in the ED, and particular hospitals where other services (e.g. echocardiography) are not easily available.

We also published the findings of a sub-study of the Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROHACT) trial which was entitled “Alignment of Site versus Adjudication Committee-based diagnosis with patient outcomes” in Clinical Trials Journal. The report addressed the important issue of the adjudication, which is now a routine part of randomized controlled trials.

During the last year, our main focus was to provide the pre-requisites for starting the HiLo-HF trial. The aim of this trial is to investigate the effectiveness of a high versus low spot of SP2 on symptoms and clinical condition and patient outcome in patients presenting to emergency departments with AHE.

In 2015, with the invaluable support that I received from my mentor and all other CVC faculty, I was successful in receiving the Alberta Innovates-Health Solutions (AIHS) graduate studentship award and the CIHR-ICRH Travel Award.

Why did you choose to work with your mentor(s)? Dr. Ezekowitz is a well-known investigator in the field of heart failure and he has contributed in many landmark studies in this specific field. I feel very lucky to be mentored by a person with that amount of impact. I also think that his way of mentorship is one of the best methods I have ever seen. He allocates a significant amount of time each week to mentoring his
numinous trainees.

Besides Dr. Ezekowitz as my main supervisor, I also had the privilege of being mentored by one of best internationally-known cardiologists in the world, Dr. Armstrong, a man with great contributions in modern cardiology. So considering my genuine interest in Cardiology and in academia, I believe this setting is the best to develop and pave my way to a successful academic life in the future.

What have you learned from working with your mentor(s)?

I have learned a lot from Dr. Ezekowitz about novel topics in the fields of heart failure management, biomarkers, risk scoring models and quality of life measures. In terms of research implementation, I have learned a lot about issues such as optimization of time-management, critical evaluation of a research question or project. I have learned much from my mentors. For example, I have learned to do research and critically evaluate a research question or project. I have learned to participate in research and coauthor papers. Through his mentorship I have been able to win many awards including the Heart Failure Society of America Young Investigator Grant.

What have you learned from working with your mentor(s)?

Dr. Justin Ezekowitz provided me with many opportunities to participate in research and coauthor papers. He also provided me with many opportunities to participate in research and coauthor papers. Through his mentorship I have been able to win many awards including the Heart Failure Society of America Young Investigator Grant.

What have you learned from working with your mentor(s)?

Dr. Ezekowitz has been an exceptional mentor. In addition to providing guidance on research, he has helped me understand the role of collaboration and developing research networks. He has provided me with many opportunities to participate in research and coauthor papers. Through his mentorship I have been able to win many awards including the Heart Failure Society of America Young Investigator Grant.

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Beyond 2000

On October 25-26, 2015 CVC hosted the 21st Annual Beyond 2000 symposia in Toronto in conjunction with the Canadian Cardiovascular Congress. Given the new guidelines allocated only two hours for the program we decided for the first time this year to hold two symposia. The first was directed towards our traditional New Concepts in Acute Coronary Syndrome topic, whereas the second addressed the unmet educational needs in the area of Heart Failure and Atrial Fibrillation. These programs were generously supported by unrestricted educational grants from AstraZeneca, Merck, Novartis, Servier and Bayer HealthCare. As has been our tradition with these events, we were pleased to have partnered with the Mazankowski/Alberta Heart Institute and the University of Alberta in undertaking this venture.

In the Acute Coronary symposium we probed new avenues in ST elevation myocardial infarction, how to reduce residual remaining risk in such patients and the most appropriate use of contemporary antithrombotic and antplatelet therapies. The symposium concluded with a futures look at how clinical trials in progress will likely affect medical practice.

The second symposium began with an assessment of novel therapeutic targets in heart failure likely to foster new drug development and included discussions around the best strategy for employing biomarkers in heart failure as well as how to integrate device therapy. The challenge of atrial fibrillation in heart failure and its implications for stroke was another major focus.

Both programs were very well received with strongly positive evaluations by the many registrants in attendance. A variety of post-event resource materials for both the ACS Symposium and the Heart Failure & Atrial Fibrillation Symposium that include interviews, recorded sessions of the lectures, and presentation slides can be found at www.Beyond2000.org

CVC Clinical Trials Colloquium

On Sunday March 8, 2015 we held the 2nd Annual CVC Clinical Trials Colloquium in Banff, Alberta in collaboration with the ACC Rockies Meetings. Thanks to the support from our Canadian sponsors AstraZeneca, Amgen, Bayer, Eli Lilly, Novartis, Pfizer, and Sanofi, we were able to host this unique event and bring together representative investigators and study coordinators from 16 sites across the country (BC, AB, MB, ON, QC, NS, NL).

This year’s Colloquium was intended to build on last year with key objectives that included (I) gaining a better understanding of all aspects of clinical trial research and participation, (II) developing strategies for choosing and executing a clinical trial successfully, (III) gaining a better understanding of legal requirements for negotiating Canadian clinical trial site agreements, (IV) discussing opportunities to enhance the overall clinical trial experience at a site level, (V) engaging in open discussion with colleagues, sponsors and CVC as it relates to challenges in participation and execution of clinical trials.

The Colloquium was expanded to not only include the main Colloquium session but also a Study Coordinator Workshop, and as part of the ACC Rockies Meeting, a Canadian VIGOUR Centre Workshop highlighting recent clinical trials results and opportunities.

Our morning agenda was ambitious but proved to be very informative. It covered the changing landscape in clinical trials, lessons learned, choosing trials wisely, costs, contract negotiations, investigator engagement, expectations and roles of the executive, steering committees and Data and Safety Monitoring Boards (DSMB) and finally, why we do clinical research. The discussion in the room generated some clear insights as it relates to each of these topics.

At last year’s colloquium, contracts were cited as one of the major contributors to delay in the start-up of a clinical trial. In an effort to address this, we invited Mark Rajakaruna, a lawyer/partner with Dentons Canada who has extensive experience in negotiating clinical trial agreements with sites, sponsors, ARO/CROs across Canada and around the world. He spoke about the contentious issues involving contracts and provided the best strategies for resolution.

In the afternoon we reconvened with the study coordinators and engaged in open sharing and discussion on ethics, electronic CRF, trial fatigue, recruitment strategies, training, sharing and discussion on ethics, electronic audits, understanding why all the data is collected on the CRF trial fatigue, and withdrawals and lost to follow up. As always our study coordinators were a wealth of knowledge and this session enabled them to share best strategies with each other, which not only reinforced what they perhaps were already doing, but also gave them some new strategies to take back to their site and work on implementing.

While all of our attendees know why they participate in clinical research, the colloquium served to remind us that clinical research gives us the opportunity to be leaders and champions in enhancing clinical practice and to beat the forefront of new research. Research not only offers us career satisfaction through intellectual curiosity but also provides opportunities for mentorship, collaboration, staff education and learning new skills. While it is clear that there are challenges that come with participating in clinical research, it is also evident that the benefits far outweigh the risks.

The Pulse of Promise

The Best of Progress
June 13, 2015 marked an extraordinary day for CVC and the University of Alberta when the Department of Medicine hosted a Festschrift to honor Paul Armstrong’s 35 years of exemplary care, discovery and mentorship as a cardiologist and the recipient of the University of Alberta’s 2014 University Cup. Borrowed from German the word Festschrift indicates an academic celebration in honor of a scholar.

The day featured presentations from four internationally renowned cardiologists whose professional lives were inextricably linked to Dr. Armstrong. It began with an overview of the Beginning of Fibrinolytic Drug Design to the Achievement of Optimal Reperfusion for ST Elevation Myocardial Infarction Patients by Frans Van de Werf, Professor of Cardiology from the University of Leuven in Belgium. This was followed by a “Big Theme” discussion of Medical Products Development by Robert Califf, formerly Professor of Cardiology and Vice Chancellor of Duke University and current Commissioner of the FDA in the United States, and Eric Peterson, Director of the Duke Clinical Research Institute who explored Novel Ways to do Clinical Trials and Health Outcomes. The academic component of the day was completed by Robert Harrington, Professor and Chair of the Department of Medicine at Stanford University who discussed how Biotech and Big Data Will Rule the World focusing on Google, Apple and IBM.

The day was capped by a gala celebratory dinner adroitly chaired by Peter Hamilton. The dinner featured tributes from several former trainees, colleagues and staff and included remarks from host, Barbara Ballermann, Chair of the Department of Medicine, Verna Yiu, Chief Medical Officer of Alberta Health Services and Richard Fedorak, Dean of the Faculty of Medicine and Dentistry.
Distinguished Visitors

In 2015, the faculty of the CVC had the privilege of hosting three outstanding, internationally renowned academics continuing a program generously sponsored by unrestricted educational grants from AstraZeneca and Novartis.

These visits are a highlight of our CVC academic year and allow for one-on-one faculty time, teaching of our cardiology and research trainees. They provide a welcome window on the global state of cardiovascular medicine as it relates to career choices for trainees and potential future directions for meaningful research. They constitute a seminal part of our educational/research mission.

DR. MICHAEL J. PENCINA
Director, Biostatistics & Bioinformatics, Professor, Biostatistics & Bioinformatics, Duke Clinical Research Institute
JUNE 2-3, 2015
• Cardiology Research Rounds: “How to Interpret Incremental Value of Biomarkers”
• Cardiology Divisional Rounds: “New US Lipid Guidelines: Main Advances and Open Questions”

Michael Pencina, a well-known leader in biostatistics and the recently appointed Director of Biostatistics and Bioinformatics at the DCRI, shared his important work on assessing the incremental value of novel biomarkers. In an ever-increasing sea of biomarkers, traditional statistical tools such as the change in the c-index are no longer sufficient in identifying meaningful biomarkers. In response to this, Dr. Pencina and colleagues developed the net reclassification index. Dr. Pencina also discussed the practical implications of the new US Lipid Guidelines: Main Advances and Open Questions.

DR. ADRIAN HERNANDEZ
Associate Professor of Medicine, Duke University Medical Center
Director, Health Services and Outcomes Research
Faculty Associate Director, Duke Clinical Research Institute
OCTOBER 20-21, 2015
• Cardiology Research Rounds: “Blueprint to Save a Failing Research Market”
• Cardiology Divisional Rounds: “Changing Care, Changing Outcomes”

Adrian Hernandez, a leader in registry and clinical trial heart failure research, presented on the importance of revitalizing the discovery to clinical impact pipeline of the research enterprise. He highlighted the key economic and clinical need to drive research as well as the importance of the patient voice and engagement. He further described the efforts of groups in the United States working on the PCORI initiative for developing and implementing pragmatic clinical trials.

DR. SONIA ANAND
Associate Director, Population Health Research Institute
Director, Population Genomics Program, Department of Clinical Epidemiology and Biostatistics
Associate Member, Department of Clinical Epidemiology & Biostatistics
McMaster University
DECEMBER 15-16, 2015
• Cardiology Research Rounds: “Ethnic Variations in Risk Factors and Burden of Cardiovascular Disease: How to prepare for the future?”
• Cardiology Divisional Rounds: “Early life origins of risk factors for cardiometabolic diseases”

We were pleased to host Dr. Sonia Anand in December 2015. She provided an insightful look at nature and nurture as part of a well-received Research Rounds entitled “Early life origins of risk factors for cardiometabolic diseases”. At Cardiology Grand Rounds she addressed the subject of “Ethnic Variations in Risk Factors & Burden of Cardiovascular Disease: How to prepare for the future?” Her visit was co-hosted by Padma Kaul and Kevin Baney and provided ample opportunities for faculty discussion and potential avenues for future collaboration.
Volume 19, No. 4  Winter 2015

Adjudication of Clinical Endpoints—Why All the Fuss?

With the arrival of the fall, I find myself constantly “out on the road” participating in various national and international scientific sessions and meetings for upcoming and ongoing clinical trials. A frequent topic of conversation raised by busy study investigators, and coordinators relates to the enormous amount of time and effort you are now investing in studies in order to identify, all potential events, capture medical record information and related source documentation (that is often hard to obtain from other health core settings), provide narratives, and compile numerous forms while under the watchful eye of the trial operational leadership.

Indeed, the use of centralised committees to adjudicate clinical events (clinical endpoint or event committees; CECs) is common in large-outcome trials, particularly for the assessment of hospital primary endpoints. Not surprisingly, site research staff are increasingly asking what is the rationale and value of this adjudication process (including the potential of source data verification) and why is it such a demanding task?

Earlier postcard randomisation outcome trials (such as the ISIS-1 study, which established the role of ASA and fibrinolysis in the management of suspected acute myocardial infarction (AMI) did not, in fact, require central adjudication; however, these studies used all cause mortality as the primary endpoint. Although no one is arguing for the need to adjudicate patient death itself, understanding the underlying cause (cardiovascular vs. non-cardiovascular) can be of added importance.

Since definitions for non-fatal events are generally heterogeneous and often times subjective, one reason for a central process of adjudication is to assist in ensuring systematic application of the endpoint definitions used in the trial. This is particularly important when determination of nonfatal events, such as peri-procedural MI, can be challenging to sort out. For example, a patient presents with an ST-segment elevation MI and is randomised to receive a treatment aimed at preventing a recurrent MI that can also potentially cause bleeding. If the patient then undergoes early PCI or coronary artery bypass surgery, does one determine whether a recurrent MI was occurred when the time-point level continues to rise within the first 24 hours of the index event? Similarly, if the patient experiences some blood loss around the time of the procedure, how do we determine whether this is a coronary bleed or is it simply an expected complication for a patient undergoing haemorrhage?

In addition, particularly in open-label trials, there is the possibility of differential misclassification, as in determining the occurrence of events based on the patient’s investigators’ label that the investigational treatment is better or worse than the comparator. By ensuring that the adjudication is done centrally, systematically, and blinded to treatment assignment, the CEC may provide protection against such differential misclassification. Regulatory authorities, including the U.S. FDA and Health Canada, derive confidence in the validity of trial results when central adjudication is performed and may therefore demand this approach before approving new treatments.

In this issue: Letter  -  Shaun Goodman

Volume 19, No. 3  Fall 2015

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In this issue: Letter  -  Shaun Goodman
Featured Presentations

Reflecting the CVC’s global reach and network of collaborators, this summary highlights some of the key national and international lectures and presentations that were delivered by CVC faculty members in 2015. The CVC’s insights and impact are enhanced by these pursuits of knowledge translation and dissemination.

KEVIN BAINEY
San Francisco, California
Transcatheter Cardiovascular Therapeutics Conference - September 2015
Invited Speaker: A Practical Stenting Issue in Multivessel Disease: When and Where to Stop?
Montreal, Quebec
Montreal Live Symposium - June 2015
Invited Speaker: Caput Divum Versus Complete Revascularization in STEMI with Multi-vessel Disease

PAUL ARMSTRONG
Mumbai, India
Fellowship of the European Society of Cardiology, Mumbai Meeting of the Fellows - September 2015
Invited Speaker: Co-Chair: Late-Breaking Clinical Sessions Deep Dive
Kingston, Ontario
Southwest Ontario Academic Medical Organization (SWAMO) Innovation Showcase, Queen’s University - May 2015
Keynote Speaker: Reflections of a Clinical Investigator
New York City, New York
Icahn School of Medicine at Mount Sinai - June 2015
Visiting Professorship Program: Acute Myocardial Infarction 2015: Reflections of a Clinical Investigator

ROBERT WELSH
Hamilton, Ontario
McMaster University/Hamilton Health Sciences - September 2015
Regional Cardiology Rounds: The Clinical Challenges of Treating Your High Risk Cardiovascular Patients Incorporating Antiplatelet Therapy Into Secondary Prevention of ACS.
London, United Kingdom
The American College of Cardiology Foundation - August 2015
Invited Speaker: Management of Acute Heart Failure - The Current and Future Role of Biomarkers in Management.
Toronto, Quebec
Heart Failure Update - May 2015
Toronto, Ontario
Canadian Cardiovascular Congress - October 2015
Invited Speaker: Emergency Department with Syncope.

PADMA KAUL
Mississauga, Ontario
Opening the Guidelines - Cardiovascular. Which Road To Take? - February 2016
Ottawa, Ontario
Ottawa Heart Failure Research Conference - October 2015
Invited Speaker: Sodium in Heart Failure.

SEAN VAN DIEPEN
San Diego, California
The American College of Cardiology Foundation - March 2016
Invited Speaker: Critical Care Year in Review for High Risk Acute Coronary Syndrome Patients: Twice as Nice or Double the Trouble?
Montreal, Quebec
18th Thrombolytic Interventional Cardiology Meeting - February 2015
Invited Speaker: From Guidelines to Practice: Oral P2Y12 Therapy in Canadian Acute Coronary Syndrome Patients.
Montreal, CA
American College of Cardiology Annual Scientific Session - March 2015
• Poster Moderator: What’s New in ACS? • Invited Speaker: Logistical Challenges in STEMI, Ship and Drip (Facilitated Transfer to PCH Hospital).
Montreal, Quebec
Canadian Cardiovascular Congress - October 2015
Invited Speaker: Reducing cardiovascular risk in patients with hypertension: Moving beyond traditional models.

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ARO Services

CVC Services and Activities

The Canadian VIGOUR Centre is recognized as a thought leader and valuable partner in cardiovascular research across all regions of Canada and amongst key centres around the world. Its track record of conducting, delivering and health outcomes is strongly influenced by clinical practice and health care.

THOUGHT LEADERSHIP
- Provide expert advice and promotion of cardiovascular research characterized by quality, scholarship and integrity
- Defined unmet needs for patients with and those at risk of cardiovascular disease
- Align new cardiovascular research with these unmet needs
- Seek cost effective solutions and enhance return on investment in research
- Trial architecture, development, data acquisition, integration, analysis, presentation and peer-review publication
- Creation of novel sub studies aimed at mechanistically informing primary clinical trial results
- Mentoring junior faculty, medical trainees, students and allied health professionals

CLINICAL TRIALS
- Investigator selection, qualification and recruitment
- Investigative site start-up and training
- Ensuring site regulatory compliance
- Project, Site, Data management
- In-house and onsite clinical monitoring (including bilingual services)

BIOSTATISTICAL ANALYSIS
- Design of research protocols and studies
- Development of statistical analysis plans and database specifications
- Data management
- Programming expertise in SAS and R
- Generation of statistical tables, figures, listings and interpretation of findings
- Consultation and execution of advanced statistical methods
- Development and application of novel statistical methods

POPULATION AND ECONOMIC HEALTH OUTCOMES RESEARCH
- Collection of resource utilization and cost data
- Development of economic models
- Cost-effectiveness analyses
- Clinical Registry development

CLINICAL REGISTRIES
Vital Heart Response (VHR): R Welsh
- Continuous Quality Improvement (CQI)
- Regional Collaboration
- Trials within registries e.g. PROACT
- Model for others

Acute Heart Failure (AHF): J Ezekowitz
- CIHR: inquiry regarding outcomes/biomarkers
- Novel Interventions/trial

EGC CORE LAB
- Informing trial design
- Monitoring protocol adherence
- Guiding mechanistic insights
- Prognosis and outcomes assessment
Clinical Trials

Our clinical trials team works hard to build and maintain strong relationships with our sites, sponsors and partners to deliver efficient, cost effective, and high quality clinical trials. In addition to the relationships we have built, we also attribute our success in the management of clinical trials to the hands on, collaborative team approach we provide to our sites, sponsors and partners which encompasses all aspects of our organization including our thought leadership, management board, project leadership, monitoring, biostatistics, health economics and administrative support teams.

We have a robust network of over 150 sites across Canada, with whom we have established relationships that have been built over many years as well as some new sites that we have been fortunate to recruit into a number of our recent studies. While we continue to focus on the operational management of phase II, phase III, and investigator initiated studies in acute coronary syndromes, lipid management, heart failure and diabetes, in 2015 we broadened our cardiovascular focus to include trials in cardiac surgery and transcatheter valve replacement (TAVR). We are continuously seeking out novel and interesting studies to be involved in and are currently in the initial planning and negotiation stages for a few new projects in 2016.

Our clinical trials team is overseen by Tracy Temple, Assistant Director of Clinical Trials, who brings a background in cardiovascular nursing, project management and 16 years of clinical research experience with the Canadian VIGOUR Centre. We have a very experienced, diverse, knowledgeable and personable clinical trials team comprised of five Clinical Trial Project Leads; two Regulatory Support staff; a Lead Clinical Research Associate; eight regionally based Monitors; a Monitoring Report Reviewer and administrative support. Responsible for ensuring all operational aspects of the study run smoothly, our Clinical Trial Project Leads and Regulatory Support staff work closely with our sites to strive for quick and efficient start-up, high recruitment and retention of patients that meet the study criteria, data entry that is accurate and well maintained, and delivery on timelines as laid out from study start-up to study completion. As the primary contact for the Canadian sites, the Clinical Trial Project Leads have their fingers on the pulse of all aspects of the trial, which enables them to maintain a good understanding of the overall functioning of the study while closely monitoring trends and issues across Canada.

In addition to conducting source document verification, drug accountability and other required monitoring related tasks, the CVC monitors use their visits as a teaching opportunity to share lessons learned and ideas from other sites which are beneficial to their daily work and also help to ensure they are audit prepared. With an extensive background in monitoring and previous involvement in many audits and inspections throughout her career with the CVC, Halina Nawrocki has helped prepare many of our sites for upcoming inspections as well as shared lessons learned with our team and sites. With the ongoing support and expertise of our project and monitoring team and well prepared sites, all CVC monitored sites who underwent inspections in 2015 received compliant ratings.

The CVC is a strong advocate of continuing education for our staff and in addition to being ICH/GCP trained, many of our team members also hold or are working toward the CCRA designation with SoCRA or the CCRA designation with ACRP. We maintain a strong focus on training and quality and encourage our teams to share their knowledge, lessons learned, and expertise on an ongoing basis in their work with sites and sponsors to help build more efficient and cost effective clinical trials in Canada.

“Medicine is the science of uncertainty and the art of probability.”

— WILLIAM OSLER
Clinical Trials

AEGIS-I

- Protocol #: CSLCT-HDL-12-77
- Sponsor: CSL Behring LLC
- Drug: CSL112
- Anticipated Timeline: August 2013-2016
- Trial Status: Target enrollment reached

A Phase 2b, multicenter, randomized, placebo-controlled, dose-ranging study to investigate the safety and tolerability of multiple doses administration of CSL112 in subjects with acute myocardial infarction.

BLAST-HF

- Protocol #: CP027
- Sponsor: Trevena Inc.
- Drug: TRV027
- Anticipated Timeline: March 2014 - April 2016
- Trial Status: Database locked and closing out sites

Randomized, double-blind, placebo-controlled, dose ranging study to explore the efficacy of TRV027 in patients hospitalized for acute decompensated heart failure.

EXSCEL

- Protocol #: BCB109
- Sponsor: AstraZeneca
- Drug: Exenatide
- Anticipated Timeline: May 2009 - June 2018
- Trial Status: Target enrollment reached now in patient retention stage

A randomized, placebo-controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus.
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Sponsor</th>
<th>Drug</th>
<th>Patient Enrollment</th>
<th>Trial Status</th>
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<td>ODYSSEY OUTCOMES</td>
<td>340/18,000 (Canada/Global)</td>
<td>Sanofi-aventis Recherche &amp; Développement</td>
<td>Alirocumab (SAR236553/REGN727)</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
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<td>LEVOSIMEDAN</td>
<td>50/760 (Canada/Global)</td>
<td>Tenax Therapeutics Inc.</td>
<td>Levosimendan</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>IMPROVE IT</td>
<td>500/18,000 (Canada (CVC)/Global)</td>
<td>Merck &amp; Co. Inc.</td>
<td>Vytorin</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>PROACT</td>
<td>600 - CANADA ONLY (Canada/Global)</td>
<td>Heart and Stroke Foundation, University Hospital Foundation &amp; Masankowski Alberta Heart Institute</td>
<td>NA</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>PROACT</td>
<td>572 CANADA ONLY (Canada/Global)</td>
<td>Heart and Stroke Foundation, University Hospital Foundation &amp; Masankowski Alberta Heart Institute</td>
<td>NA</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>PROCT</td>
<td>614/14,000 (Canada/Global)</td>
<td>Novartis</td>
<td>Ezetimibe/simvastatin</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>SODIUM-HF</td>
<td>1,000 (Canada/Global)</td>
<td>CIHR grant</td>
<td>Sitagliptin</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>SODIUM-HF</td>
<td>157/167 (Canada/Global)</td>
<td>CIHR grant</td>
<td>Sitagliptin</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>TECOS</td>
<td>28/161 (Canada/Global)</td>
<td>Merck &amp; Co., Inc.</td>
<td>Sitagliptin</td>
<td>Patient enrollment target</td>
<td>Patient enrollment achieved to date</td>
</tr>
<tr>
<td>TECOS</td>
<td>549/14,745 COMPLETED (Canada/Global)</td>
<td>Merck &amp; Co., Inc.</td>
<td>Sitagliptin</td>
<td>Database locked and sites closed</td>
<td>Patient enrollment achieved to date</td>
</tr>
</tbody>
</table>

Note that the 500 for Canada is based on original projections and sample size and does not reflect modified sample size.
Diabetes Comes of Age in Cardiovascular Medicine: The TECOS Study

By Paul W. Armstrong

The year 2015 marked the culmination of seven years of work on the TECOS trial (Trials Evaluating Cardiovascular Outcomes with Sitagliptin), a large pragmatic international study designed to assess the impact of sitagliptin versus placebo on cardiovascular events. This intervention was added to usual diabetes care and undertaken in nearly 15,000 patients with type 2 diabetes who already had an established cardiovascular disease.

The TECOS trial was an academic collaboration involving the Duke Clinical Research Institute, the Canadian VIGOUR Centre and the Oxford Diabetes Trials Unit. The trial represented a unique collaboration between endocrinology and cardiology with three thought leaders from each specialty represented on the executive committee. Along with the sponsor, we crafted the protocol, oversaw the operations of the trial and then examined the results after an average follow up of three years in April of 2015. The results were presented at the American Diabetes Association in Boston in June 2015 and simultaneously published in the New England Journal of Medicine.

Much to our satisfaction and great relief, sitagliptin proved to be safe and effective in controlling glycaemia in these diabetic patients. Most importantly, it did not aggravate heart failure or other ischemic end points over the three years of follow up care as had been suggested previously with a number of diabetes drugs, including one within the class of Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors) where sitagliptin resides. Because diabetes is growing in epidemic proportion in association with obesity, and as such is a major cause of heart disease and stroke as well as kidney, eye and nerve damage, new therapies and approaches are desperately needed. This need demands new forms of collaboration such as occurred in the TECOS trial. We were very pleased to have engaged 26 sites across Canada who enrolled 5,459 patients, exceeding our enrollment goal. I wish to credit Tracy Temple and Lyndsey Garrity for their operational leadership so critical to this achievement and our collaborators across Canada who did an outstanding job.

Of particular interest in this trial was the issue of heart failure which was suggested as a potential hazard with a similar drug in the same class. Heart failure in diabetic patients is particularly harmful with a mortality double that of non-diabetic patients, and has been characterized as “frequent, forgotten and often fatal”. We were pleased to have had the opportunity to present this work to our Canadian colleagues at the Late Breaking Session of the Canadian Cardiovascular Society meeting in October 2015, as well as at a special investigator meeting in Toronto on that same occasion.

It is important to note that there are several other lessons to be learned from the large enriched database we have acquired. We are exploring, as one example, the question of osteoporotic based fractures that are known to be in excess in diabetes. Other questions include the impact on the elderly and the role of hypoglycemia in aggravating ischemic end points to name a few. Since diabetes drugs are rapidly changing, and as a number of new agents are now in development, it is likely this patient population will be a target for future collaborative studies that are unquestionably enriched by novel collaborations as defined in the TECOS study.
Patients with chest pain are often seen first by an ambulance and taken directly to an emergency department where ECGs, blood tests and clinical evaluations occur in order to understand the source of their chest pain. The majority of this investigation is directed at the diagnosis of a heart attack. Recent advances in a biomarker called troponin have made this more rapidly and readily available and now even on smaller point-of-care (POC) devices. The PROACT-4 trial evaluated a strategy of testing troponin in the ambulance using a novel (POC) device. Paramedics in the Edmonton zone were able to obtain patient consent and randomize in the field. Using a small sample of blood, inserted into the mobile POC device, meant that the results of the heart test troponin could be available in less than 15 minutes. The trial was designed to be very pragmatic with broad inclusion criteria and few exclusion criteria. It also was designed to mimic the clinical practice of how paramedics and emergency department clinicians function.

This was truly a homegrown clinical trial that involved clinicians from each of the hospitals in Edmonton, paramedics across the zone and Alberta Health Services as partners in testing the strategy for patients with chest pain. Funding was received from the Heart and Stroke Foundation of Canada, the University Hospital Foundation, the Mazankowski Alberta Heart Institute and in-kind funding from Alberta Health Services together with Alere Inc. This partnership between the hospital and health system, ambulances, academics, industry, patients and clinicians is critical for the advancement of human health. This is where we as the Canadian VIGOUR Centre sit at the interface.

After 18 months of enrolment, the education of hundreds of paramedics and inclusion of 601 patients, the trial was presented at the 2015 American Heart Association (AHA) Scientific Sessions in Orlando, Florida as a late breaking clinical trial presentation. The primary endpoint which was the time from an ambulance arrival on scene to the time the patient was discharged from the emergency department was shorter for those receiving the point of care troponin in the ambulance. Patients in the point of care troponin arm spent a median of 8.8 hours from ambulance to discharge; the usual care arm spent 9.1 hours for the same time. This was statistically significant and lead to detailed discussion on the clinical relevance. We were able to shorten the time to first troponin availability by nearly 100 minutes yet were not able to translate this full reduction to overall time. Furthermore, there were no differences in any of the secondary points which were traditional. We spent a fair amount of time thinking about the problem we were tackling and the data we collected so we had a look in greater detail at our results. First, we identified that we had enrolled a broad group of patients with chest pain and these were not low-risk patients. Second, we determined that some patients were not tested as intended (no troponin in the ambulance) and this may have led to the inability to demonstrate a greater time difference. Third, and what was the primary focus for the AHA discussant of our trial, was that we used a relatively sensitive troponin assay but not the newest high sensitive troponin. Finally, the majority of patients were discharged directly from the emergency department and this highlighted an important need to have an upfront troponin. Since most people were low-risk and did not have an acute coronary syndrome, yet spent a large amount of time in emergency department, any methods to reduce this amount of ‘dwell time’ would lead to significant health care savings. Even within our clinical trial we estimated that 15,000 hours of emergency department time would have been saved if troponin was done in the ambulance for all patients.

What does this mean overall? Broad engagement in a clinically relevant question with the right stakeholders engaged can lead to scientific advancement. As we answer one question we have raised several others, including further inquiries about system integration and POC biomarkers in the acute care environment. We look forward to answering these and other questions with you as a partner.
CVC has an extensive site network across Canada of principal investigators (PIs) who actively participate in CVC managed clinical drug trials, to meet patient enrollment targets. This map represents the locations of 124 principal investigators who were participating in ten (10) of the active clinical trials either coordinated by the CVC, or monitored by the CVC, in 2015. Nearly 50% of these sites have participated in more than one CVC managed clinical trial.
The aim of our ECG Core Laboratory is to translate research results into clinically relevant applications. Using the ECG – a venerable but powerful biomarker – we can generate an improved understanding of the pathophysiologic processes involved in acute coronary syndromes (ACS), thereby enabling not only prediction of outcomes but also assessing effectiveness of treatment. These insights serve to further stimulate cardiovascular scientific research.

Key projects the ECG Core Lab is involved in include the Vital Heart Response and PROACT-4 studies.

The Vital Heart Response (VHR) project led by Dr. Robert Welsh is a regional initiative that aims to implement timely evidence-based reperfusion strategies to maximize the outcome of patients with ST-segment elevation myocardial infarction (STEMI). VHR project has enrolled 3,578 patients and the Core Lab has completed analysis of 3,333 patients (over 9,000 ECGs).

In 2015, the ECG Core Lab was also involved in PROACT-4, the fourth stage of the PROACT project. A key component of this study is timely recognition of acute cardiovascular patient presentations and how best to provide rapid early diagnosis and more efficient patient care. In 2015, 210 patients’ ECGs were analyzed and this data will be examined in concert with acute biomarkers from patients with acute chest pain as well as those with shortness of breath and presumed heart failure.

The ECG Core Lab at the CVC continued its mandate of conducting quality analyses using clinical research data in 2015. The Core Lab has accumulated a wealth of experience and continues to serve as a valuable resource and training ground for the next generation of talented researchers. To date ECGs from over 74,600 patients enrolled in studies around the world have been analyzed. This provides an excellent database for additional sub-studies, analyses and research.

Pushpa Jagasia, MD - Senior ECG Reader  
Sheila Li, MSc - ECG Reader
The Pulse of Promise The Beat of Progress

If “creativity is intelligence having fun” (acc. Albert Einstein), then the CVC Biostatistics Group had a year of good fun with a variety of statistical methods. Services provided by the Group include study design, data management, development of statistical analysis plans and database specifications, programming expertise in SAS and R, generation of statistical tables, figures and listings and interpretation of findings, and consultation and execution of advanced statistical methods.

POPULATION HEALTH LABORATORY

Drs. Anamaria Savu and Padma Kaul addressed the intersection of health and wealth among Canadians; specifically, the association between personal bankruptcy filing and acute myocardial infarction (AMI) rates from 2002 to 2009.1 Cross-lagged statistical methods were used to assess this longitudinal relationship with adjustment for socioeconomic factors. As hypothesized, they observed that regions with higher rates of AMI were related with higher rates of bankruptcy.

Drs. Savu and Kaul also conducted an interrupted time series analysis to examine the relationship of the 2007 American Heart Association prophylaxis guidelines on infective endocarditis (IE) hospitalizations.2 Based on the Canadian Institutes for Health Information discharge abstract database to identify all IE hospitalizations between 2002 and 2013, they found that the published guidelines did not change the rate of increasing IE hospitalizations.

CLINICAL TRIALS

The primary results of the PROACT-4 and SODIUM-HF trials were published with Mr. Yinggan (Gray) Zheng leading these analyses. In PROACT-4, patients were randomized to usual care (troponin testing in the emergency department) or point-of-care troponin testing, with the hypothesis tested that point-of-care troponin testing could expedite care for chest pain patients presenting in the emergency department and/or by ambulance.3 Although there were no observed associations with outcomes, it demonstrated the opportunity to improve the process of care.

The SODIUM-HF pilot study was designed to test the feasibility of implementing a low-sodium dietary intervention in patients with heart failure and to assess the change of brain natriuretic peptide levels and quality of life (as per the Kansas City Cardiomyopathy Questionnaire) at six months.4 Mr. Zheng and colleagues observed that improvements in these metrics were observed in patients who had achieved target dietary sodium levels.

Two secondary analyses of clinical trials highlighted the use of emerging methodology and a unique clinical metric. First, the choice of arterial access site for percutaneous coronary intervention and its association with the risk of major bleeding was examined in acute coronary syndrome (ACS) patients enrolled in the TRACER trial.5 Dr. Cynthia Westerhout was involved in this study, which used inverse probability weighting to account for this non-randomized selection of access site (transradial versus transfemoral access). And second, Dr. Westerhout and colleagues examined frailty, a rarely measured condition, in a large-scale ACS cohort from the TRILogy-AcS trial.6 Frailty was based on the Fried Score, which was self-reported at baseline in patients ≥65 years, and was associated with increased risk of cardiovascular death, MI, or stroke.

2 Mackie AS, Liu W, Savu A, Marelli AJ, Kaul P. Infective endocarditis hospitalizations before and after the 2007 American Heart Association prophylaxis guidelines Citation: CANADIAN JOURNAL OF CARDIOLOGY.
Population Health and Economic Outcomes

In the last decade over half a million Albertans have been diagnosed with heart disease, which accounts for the second highest number of deaths in the province annually. Ongoing technological advances in the treatment of acute coronary syndromes and heart failure make it essential to examine whether the use of these expensive drugs and devices is equitable and to assess their impact on current and future costs of cardiac care in Alberta.

The CVC continues to be actively involved in examining population-level issues related to access, delivery, treatment, and outcomes of heart disease in Alberta and Canada. Administrative databases have become a cornerstone in the process of assessing performance and providing feedback to improve quality of health care delivery at population-level. Accordingly, the CVC has one of the largest repositories of cardiovascular data at the University of Alberta. This repository currently includes data on approximately 6.5 million hospitalizations for 2.5 million Canadians, and data on hospitalizations, outpatient care, medications, and vital status for over 900,000 Albertans suffering from heart disease over the last decade. This data has been used to examine several research questions including socio-economic and urban/rural differences in access to treatment and outcomes; outcomes among vulnerable populations including women, the elderly, and ethnic minorities; the association of risk factors and use of evidence-based therapies on long-term outcomes; impact of alternative levels of care; resource utilization and costs of care; validity and reliability of disease coding; and novel methods to risk-stratify patients.

Business Office

The business office is fundamental to the organizational and financial underpinnings of the CVC. Reviewing and negotiating contracts is one of its key tasks, alongside providing expert service in the areas of managing agreements, developing and tracking metrics, and executing invoices and site payments. Dedicated to financial stewardship, the business office prudently manages revenue and expense administration. It is also committed to the progress of information systems management, strategic planning, process improvement, and the promotion of learning and development initiatives. The business office is responsible for the creation and distribution of all marketing materials aimed at creating strong brand awareness that speaks to the mission and values of this organization. Finally, the office facilitates communications between the CVC and many institutional partners, which include, but are not limited to, Duke Clinical Research Institute (DCRI), Alberta Health Services (AHS), and Northern Alberta Clinical Trials and Research Centre (NACTRC). Our dedication to upholding strong partnerships with these institutions is essential to the day-to-day operations of the CVC.

“For medicine, the greatest surprises lie still ahead of us, but they are there waiting to be discovered or stumbled over sooner or later.”

— LEWIS THOMAS
Our CVC Faculty are internationally recognized as Thought Leaders in their respective areas of interest. They represent a unique and dynamic integration of clinical research. The approach begins by addressing unmet clinical needs through conducting rigorous clinical investigation and clinical trials of novel diagnostic and therapeutic interventions in selected areas of cardiovascular medicine. It extends from that pivot to the knowledge gained through detailed registries of all patients in areas of particular interest and relevance to public health, namely Acute Coronary Syndromes and Heart Failure. Our group has been especially keen to explore better ways of analyzing the responses of patients to interventions by modeling their outcomes over time, taking account of the relative value patients put on differing outcomes and their implications for quality of life and health care costs. Finally we are well positioned to study health care outcomes at a population level for all Albertans to assess how well new advances are being applied and whether they are making a meaningful difference.

**PAUL W. ARMSTRONG, MD**
- Founding Director, Canadian VIGOUR Centre
- Distinguished University Professor, Division of Cardiology, University of Alberta
- Formerly Chair of the Department of Medicine, University of Alberta
- Founding Director of TORCH (Tomorrow's Research Cardiovascular Health Professionals), a Strategic Training Program Initiative
- Founding President of the Canadian Academy of Health Sciences

*Dr. Armstrong’s research interests include:*  
- Development of novel methods to enhance clinical trial methodology  
- Cardiovascular disease and its implications in the elderly  
- Pathophysiology and novel therapeutic approaches of congestive heart failure  
- Diagnosis and management of acute coronary syndromes, with emphasis on timely interventions  

**JUSTIN EZEKOWITZ, MBCH, MSC**
- Co-Director, Canadian VIGOUR Centre  
- Associate Professor, Division of Cardiology, University of Alberta  
- Director, Heart Function Clinic, Mazankowski Alberta Heart Institute  
- Alberta Innovates - Health Solutions Population Health Investigator

*Dr. Ezekowitz’ research interests include:*  
- Testing the impact of drugs and processes of care for patients with acute heart failure  
- Novel interventions for patients with chronic systolic and diastolic heart failure  
- The impact of comorbidities such as atrial fibrillation, anemia and hip fractures in patients with heart failure  
- Knowledge gaps for drugs and process of care in heart failure.

**SHAUN GOODMAN, MD, MSC**
- Co-Director, Canadian VIGOUR Centre  
- Associate Professor, Division of Cardiology, University of Alberta  
- Founding Director of TORCH (Tomorrow’s Research Cardiovascular Health Professionals), a Strategic Training Program Initiative  
- Heart & Stroke Foundation of Ontario (Polo) Chair and Professor, Department of Medicine, University of Toronto  
- Adjunct Professor, Department of Medicine, University of Alberta

*Dr. Goodman’s research interests include:*  
- Facilitating clinical trial, observational, and knowledge translation research in cardiovascular disease in Canada with a focus on:  
  - Diagnosis, management, and prognosis of acute coronary syndromes  
  - Optimal stroke prevention risk stratification and management in atrial fibrillation  
  - Primary and secondary prevention of cardiovascular disease.
KEVIN BAINÉY, MD

• Assistant Professor and Interventional Cardiologist, Mazankowski Alberta Heart Institute, University of Alberta
• Director, Interventional Cardiology Fellowship Program, Mazankowski Alberta Heart Institute, University of Alberta

Dr. Bainey’s research interests include:
• Optimizing reperfusion in ST-elevation myocardial infarction
• Ethnic-based clinical outcomes

PADMA KAUL, PHD

• Director, Outcomes Research, Canadian VIGOUR Centre
• Associate Professor, Department of Medicine, University of Alberta
• Adjunct Assistant Research Professor, Duke University Medical Center
• Adjunct Associate Professor, School of Public Health, University of Alberta

Dr. Kaul’s research interests include:
• International differences in practice patterns and outcomes
• Sex differences in treatment and outcomes of cardiovascular disease
• Long term chronic disease implications for pregnancy related complications
• Issues related to access and delivery of care at a population level
• Health economics.

FINLAY A. MCAFIST, MD, MSC

• Professor of Medicine, University of Alberta
• Director, Patient Health Outcomes Research and Clinical Effectiveness Institute, University of Alberta
• Senior Health Scholar, Alberta Innovates - Health Solutions (2010 - 2017)
• Capital Health Chair in Cardiovascular Health Outcomes
• Past-Chair, Outcomes Research Task Force, Canadian Hypertension Education Program
• Past-President, Canadian Society of Internal Medicine

Dr. McAlister’s research interests include:
• Outcomes research in hypertension, heart failure, perioperative care, and coronary artery disease
• Clinical epidemiology methodology with a focus on evidence-based medicine and implementation of evidence at the bedside
• Methodology of trials and systematic reviews

SEAN VAN DIEPEN, MD

• Assistant Professor of Critical Care Medicine, Division of Critical Care Medicine, University of Alberta
• Academic Cardiologist-Intensivist

Dr. Van Diepen’s research interests include:
• Critical care cardiology
• Cardiovascular surgical care
• Cardiovascular risks of cardiac and non-cardiac surgery and heart failure

ROBERT WELSH, MD

• Professor, Division of Cardiology, University of Alberta
• Edmonton Zone Medical Director, Cardiac Sciences
• Interventional Cardiologist, Mazankowski Alberta Heart Institute
• Director, Adult Cardiac Catheterization and Interventional Cardiology Program
• Vice-President, Canadian Association of Interventional Cardiologists
• Co-chair of Vital Heart Response
• Co-chair of the Mazankowski TAVI Program

Dr. Welsh’s research interests include:
• Acute Coronary Syndromes and Interventional Cardiology
• Cardiovascular disease and diabetes
• Exercise physiology and cardiac physiology
• Pre-hospital management of STEMI and the interaction of pharmacological (antiplatelet and fibrinolytic) and mechanical interventions (primary and rescue angioplasty).
Worldwide Collaborators

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Sao Paulo, Brazil

CS RESEARCH, CLEVELAND CLINIC
Cleveland, USA

DUKE CLINICAL RESEARCH INSTITUTE
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FLINDERS MEDICAL CENTRE
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LEUVEN COORDINATING CENTRE
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ICAHN SCHOOL OF MEDICINE, MOUNT SINAI
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Uppsala, Sweden

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• the CVC faculty, external advisors and collaborators for their contributions and for providing ongoing research opportunities, we look forward to providing continued services and to future collaborations;
• the CVC staff and management for their dedication, professionalism, excellent contributions and ingenuity that enhances the quality of our research work;
• our trainees for their commitment and enthusiasm as the next generation of researchers;
• the sponsors and granting agencies, without their financial support these trials and educational activities would not be possible;
• the excellent work of Ellen Pyser and her colleagues Carla Price and Oksana Grant for their time and the dedication required to produce this report;
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• photographers Matthew Martin and Stephen Wreakes for many of the images enclosed in this report;
• McCallum Printing Group Inc. for their service in printing this report and our Chronicle newsletter.
“You cannot swim for new horizons until you have courage to lose sight of the shore.”
— WILLIAM FAULKNER