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Principal investigators (PIs) and study coordinators (SCs) from 12 sites and 7 provinces, together with medical representatives from Canadian pharmaceutical, met to discuss regulatory, ethical, operational, and legal issues related to, and share their experiences and best practices in, conducting clinical trials.

One of the key objectives of this year’s Colloquium was to enhance the understanding of PI roles and responsibilities in clinical trials and what PI oversight means in the context of clinical research expectations and regulations. The results of a pre-Colloquium survey of participating sites suggested that 75% of sites had experienced an audit, and among those that had previously undergone inspections by regulatory authorities (Health Canada and the U.S. Food and Drug Administration), PI oversight was a frequent area of scrutiny.

As indicated by the U.S. FDA Code of Regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH; i.e., Good Clinical Practice [GCP])--and highlighted in a recent DCRI PI Oversight document shared with you--the PI is the leader of the local clinical research team and assumes complete responsibility for the safe and successful execution of the protocol.

This includes a number of responsibilities and duties that can only be accomplished when the PI is an active and engaged leader in the conduct of the trial: (1) protocol knowledge; (2) oversight of the patient consent and randomization process; (3) trial follow-up, study drug compliance, and patient retention procedures; (4) complete ascertainment of suspected trial endpoints and adverse events; (5) local ethics board reporting; (6) reporting of significant GCP issues; (7) resolution of Corrective Action Plans (CAPs) put in place when issues are identified during trial conduct; and, (8) participation in monitoring activities.

This exhaustive (and sometimes exhausting!) list of PI responsibilities clearly demands a local oversight plan, including defined responsibilities, awareness and good communication (e.g., weekly reviews with the study coordinator), involvement of sub-investigators, frequent engagement with, and providing ongoing access to, study coordinators and patients. Thus, in the face of a high likelihood that your clinical trial oversight will be examined under the microscope, the Scouts Canada motto “Be Prepared” offers up some good advice!

Shaun Goodman
CVC Co-director

"Dr. Simpkins drew the short straw at the pre-inspection meeting!"
As noted by Dr. Shaun Goodman in his cover letter, on March 12, 2017, the Canadian VIGOUR Centre (CVC) welcomed 12 Canadian sites, representing 7 provinces across Canada, to participate in the 4th Annual CVC Clinical Trials Colloquium in Banff, AB. In preparation for this year’s colloquium our selected sites, the majority of whom had not previously attended the colloquium, were tasked with completing a 30 question survey which guided many of our presentations and discussions throughout the day.

The 3 primary objectives were to (1) work together to enhance best practices in conducting clinical trials locally and across Canada through an open forum discussion and sharing among clinical trial sites, the CVC and industrial sponsors, (2) establish and understand the roles and responsibilities of the investigators in clinical trials and what investigator oversight means within the context of clinical research expectations and regulations, and (3) share and gain knowledge from current and past clinical trial experiences in order to achieve success in all aspects of future clinical research studies.

Based on feedback from prior years as well as key areas of interest identified through the CVC’s work with sites and sponsors, our agenda was centered on the following four topics: feasibility, legal aspects of clinical research agreements, audits, and investigator oversight. Facilitated by CVC Assistant Director of Clinical Trials, Tracy Temple, and CVC Co-directors, Dr. Shaun Goodman and Dr. Justin Ezekowitz, this was a unique opportunity to ask questions, strategize on topics; and share, through open discussion with colleagues, our agenda focused on the sponsor, the second more focused on process and safety throughout a patient's participation in a study, and the third more focused on process and safety throughout the lifetime of a project. Recognizing the increasing costs associated with study start up for both the site and sponsor and understanding that traditionally the top 25% of the participating sites are the ones who contribute the majority of recruitment, it was clear that the need to thoroughly assess all aspects of feasibility before moving forward with a study is important. Access and usage of data warehouses to screen for potential patients was clearly split among the group with many facing ongoing challenges centered on privacy, accessibility, ineffective systems, and costs associated with access.

Recognizing the importance of ascertaining all clinical events and safety throughout a patient’s participation in a study, accessibility and review of the electronic medical record (EMR) has become invaluable in capturing missed events and safety which the patient may not have recalled. While many sites do not have issues accessing the EMR for recruited study participants it was clear that other sites had restrictions which made it difficult for them to easily access this information. With the emergence of EMR’s across the country and the importance within a clinical trial to ascertain all clinical events and safety, accessibility to EMR’s to follow.

The 4th Annual CVC Clinical Trials Colloquium was a research patient is critical and should be negotiated with your institution. Incorporating language which speaks to this in the patient informed consent will become increasingly important moving forward.

This year we welcomed back Marlon Rajakaruna, a partner at Dentons who brings extensive legal knowledge and expertise as it relates to clinical trial research agreements. Marlon shared his insights on the top 10 risks within clinical research agreements and confidentiality agreements. In response to our survey it was highlighted that many sites do have confidentiality counsel available to review their clinical trial research agreements.

Marlon explained the importance of having legal counsel review the contract to not only ensure a good understanding of what your insurance covers but to also identify loop holes that exist especially within the indemnity section of an agreement. Also highlighted was the importance of educating yourself on foreign legislation specific to the governing law and jurisdiction sections as well as ensuring jurisdiction is within Canada in order to maintain your insurance coverage. While Marlon’s presentation was not intended to provide legal advice, it did help to inform us about some of the key risks associated with clinical research agreements and the importance of legal review.

Pulling in the expertise from those who have had first-hand experience with audits from the FDA, Health Canada and sponsors we were able to identify a number of common themes. Lisa Berdan, Director of Mega Trials at the DCRI reminded us of the importance to always be prepared. She highlighted some of the key deficiencies noted in site audits including: a failure to follow an investigational plan and/or regulations, protocol deviations, inadequate record keeping, inadequate accountability of investigational product, inadequate communication with ethics, inadequate subject protection including reporting of safety. Lisa also reminded us of the importance of utilizing your primary source documents (medical records, lab reports, etc.) and not transcribing information to a secondary source. With the changing landscape in clinical research it is critical to ensure quality systems are in place with local oversight plans.

Two of our sponsor representatives, Lynn Breakwell (Sanofi) and Linda Allen (Bayer) walked us through the “dos and don’ts” of audits. Tracy Temple laid out what to expect with a Health Canada inspection and Noreen Lounsberry from Victoria, BC then shared her local experience with audits and noted the changing focus with each inspection; the first more focused on the sponsor, the second more focused on process and calibration records, and a third focused on PI oversight and training.

Rounding out our audit discussions, it was a pleasure to have Dr. Zubin Punthakee and Tracy Tazesco from Hamilton share their FDA audit experience which highlighted the importance of the sponsor’s/ARO’s involvement as well as the importance of having systems that are easy to follow and understood by their local team.

As noted in Dr. Shaun Goodman’s cover letter (see page 1), investigator oversight remains one of the most important aspects of participating in clinical research and this was a repeated theme embedded in all aspects of our Colloquium (and ongoing communications with our sites).

We can only bring a small group of sites to the Colloquium each year. However, we hope that ongoing efforts to disseminate this key information to others through our Chronicle, and peer-to-peer communications you have, including with our Project Teams and monitors, will highlight the importance of choosing participation in trials wisely, mitigating risk with your clinical trial site agreements through consultation with legal counsel, always being prepared for audits and inspections, and ensuring you are an involved and informed investigator.

We would like to thank the sites who contributed to the success of this meeting as well as our Canadian sponsors, AstraZeneca, Amgen, Bayer, Novartis, Pfizer/BMS Alliance, and Sanofi, for their support which enabled us to host this unique opportunity. Recognizing the abundance of information we gathered during this one day meeting, we look forward to continuing to share additional learnings with you in future issues of the Chronicle.

If you are interested in hearing more about the Colloquium or participating in a future Colloquium please contact Tracy Temple @ tracy.temple@ualberta.ca or 780-492-1876.
Building on the first study, STREAM-2 is a Phase 4 multi-national trial on strategic reperfusion in elderly patients with acute myocardial infarction. This is an investigator-initiated study sponsored by Leuven Research and Development at the University of Leuven, Belgium and Co-chaired by Dr. Frans van de Werf and Dr. Paul Armstrong.

STREAM-2 will randomize acute ST-segment elevation myocardial infarction patients >70yrs within 3 hours of symptom onset in a pre-hospital or emergency department of a community hospital that cannot reliably undergo primary PCI within 60 minutes of ECG diagnosis.

In Canada this study will be undertaken in the Edmonton, Alberta region and is a unique collaboration between pre-hospital emergency medical professionals, community hospitals and the PCI centres. The trial plans to enroll 600 patients globally with recruitment expected to start in the coming months. In Canada we have recently received Health Canada approval and are actively undergoing ethics review. We appreciate all the hard work to activate this study in Edmonton and look forward to the first Canadian patients being recruited.

If you are interested in further information regarding this trial, please contact Clinical Trial Project Lead, Courtney Gubbels at 1-800-707-9098 ext 2 or via email at courtney.gubbels@ualberta.ca or Regulatory Specialist Kalli Botseck, ext 6 or via email at kalli@ualberta.ca.

The SODIUM-HF trial currently has 360 subjects randomized (31-Mar-2017) at 19 sites in Canada, Chile, Mexico and New Zealand. Thank you to all the sites for your continual hard work and efforts in identifying, enrolling and retaining study patients. We look forward to activating additional sites in Canada and Australia in the coming months.

Thank you to all site personnel who joined the recent Dietitian Working Group Teleconference on February 2. If you were unable to attend, please review the February Trial Newsletter for study updates and FAQs minutes. We also featured Dr. Escobedo's site from Mexico City in our latest newsletter and look forward to profiling other SODIUM-HF sites to “meet” and learn from each other.

We would also like to remind all sites about the ongoing Winter/Spring Enrolment Challenge that will take place from 02-Feb-17 to 02-May-17 across the following 4 main geographic areas: Central and Maritimes, Prairies, West Coast and International. The “team” that has the greatest (relative) increase in the monthly enrolment average as of May 2, 2017 will receive “special kudos”! Winners will be announced during the May Dietitians Working Group call. Further information on the challenge can be found in the SODIUM-HF newsletter.

The Dietitian Tools Video was also recently sent to all sites. The video contains useful tips shared by Liz Woo (dietitian at Dr. Ezekiwitiz’s site) for teaching patients about the SODIUM-HF dietary intervention. If there are any tools your site uses that you have found particularly helpful for patients, please share these with Nubia Zepeda. These tips will be included in the upcoming study newsletter.

If you are interested in further information about the SODIUM-HF trial, please contact the Clinical Trial Project Lead Nubia Zepeda at 1-800-707-9098 ext 8 or via email at nzepeda@ualberta.ca.
LEVO-CTS

Recognizing the hard work of the US and Canadian sites along with the 882 patients who volunteered to participate in the LEVO-CTS trial, on Sunday, March 19, 2017 during the Late Breaking Clinical Trials session at the American College of Cardiology conference in Washington, DC, Dr. John Alexander from the Duke Clinical Research Institute presented the study results.

The primary objective of the study was to compare the efficacy and safety of levosimendan with placebo in patients with reduced LV function undergoing cardiac surgery with cardiopulmonary bypass support.

The final results showed that "levosimendan, given prophylactically prior to cardiac surgery to patients with reduced left ventricular function, had no effect on the co-primary quad outcome of death, dialysis, MI, or mechanical assist device use; or the dual outcome of death or mechanical assist device use. However, levosimendan was effective and safe as an inotrope to increase cardiac output in patients at risk for perioperative low cardiac output syndrome.”

While the study did not meet its primary outcomes, there was a "nonsignificant between-group difference in mortality through 90 days” with the data suggesting that “prophylactic levosimendan may have the potential to prolong survival among patients at risk for undergoing cardiac surgery.”

Full details on the study results can be found in the simultaneous publication from March 19, 2017 in the New England Journal of Medicine:


There is still much to be learned from the data collected and secondary analyses are being planned in the near future.

We would like to extend our gratitude to the Canadian investigators and Study Coordinators who did an amazing job throughout this trial. The Canadian recruitment was robust, with 160 patients randomized from our 10 participating sites, many who exceeded their projected enrollment target. In addition to the outstanding recruitment, the Canadian sites went above and beyond to ensure the data was query-free and ready to be locked with very tight deadlines.

A special shout out to our top 3 enrolling Canadian sites, who along with the other 7 Canadian sites successfully utilized all available drug supply in Canada and had to conclude recruitment early:

#1: Dr. Kalavrouziotis, Nathalie Gagne and Hugo Tremblay from Quebec, QC - 31 patients.

#2: Dr. Nagpal and Stephanie Fox from London, ON - 29 patients.

#3: Dr. Bozinovski and Sheryll Sorensen from Victoria, BC - 22 patients.

It has truly been a pleasure working with our Canadian sites on this trial and we look forward to working with you again on future cardiac surgery trials!

For further information regarding this trial, please contact Clinical Trial Project Lead, Jodi Parrotta at 1-800-707-9098, ext. 3 or by email at jodi.parrotta@ualberta.ca.

Sponsored by Tenax Therapeutics, Inc., LEVO-CTS is a Double Blind, Randomized, Placebo-Controlled Study of Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass.

ClinicalTrials.gov identifier: NCT02025623

ODYSSEY OUTCOMES

Welcome to spring!

It’s going to be a busy year for ODYSSEY Outcomes as this is expected to be the final year of the study. To prepare and ensure closeout is as smooth as possible the focus will continue to be on patient retention in addition to data cleanliness and maintenance of regulatory documents.

We will continue to follow up with all sites who have patients that have temporarily or permanently stopped study drug. We appreciate all of your efforts to maintain the connection with these patients and ensure they continue to be followed for the duration of the study. Every patient counts and at the very minimum we need to obtain a vital status on all patients.

Remember, if a patient withdraws consent for everything except a final medical chart review or a phone call at the end of the study, then that patient is NOT considered to have “withdrawn consent”. For any Lost to Follow-Up (LTFU) patients, every effort must be made to locate that patient, and just as important, all efforts need to be documented, to show that ongoing searches took place.

Please be sure to have all of your patients sign the new addendum linked to Amendment 11, and as usual, document this process in the patient’s chart.

Recently updated documents include a new Lab Manual, as well as a new Investigator’s Brochure. Please be sure to complete the IB acknowledgement form, and return a copy to CVC via email. Originals are to be maintained at the site.

For each patient, Covance Lab Kits are replenished automatically based on completion of a prior visit. However, if you find your site does not have a kit for an upcoming visit, please place a manual order for the one required kit, and allow up to 10 business days for it to arrive. Please continue to check your kit inventory regularly, and remove any expired/damaged kits.

Thank you for promptly addressing your open queries and/or missing pages. Please let CVC know if your site investigator is experiencing any issues accessing the eCRF, or within the eCRF to sign any required pages (such as SAEs and AESI with immediate notification).

When there are queries for source documents, please be sure to note who is requesting them (CEC vs Safety) and where they need to be sent. If you are not sure where each of these need to be sent please contact Jodi.

If you have any questions about this trial, please contact Clinical Trial Project Lead, Jodi Parrotta at 1-800-707-9098, ext. 3 or by email at jodi.parrotta@ualberta.ca.

Sponsored by Sanofi-aventis Recherche & Development this is a randomized, double blind, placebo-controlled, parallel-group study to evaluate the effect of Alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an Acute Coronary Syndrome.

ClinicalTrials.gov identifier: NCT01663402
The Canadian VIGOUR Centre is pleased to be collaborating closely with the Duke Clinical Research Institute and Luitpold Pharmaceuticals, Inc. on a new clinical trial testing a novel investigational therapy for patients with heart failure. HEART-FID plans to enroll just over 3000 heart failure patients, with reduced ejection fraction and iron deficiency, at approximately 200 sites in North America. We are actively searching for Canadian sites that would be interested in participating in this exciting trial involving the administration of intravenous (IV) ferric carboxymaltose (FCM) compared to placebo.

For sites that we have already approached we look forward to completing feasibility by the end of April and moving forward with ethics submissions, regulatory and contracts to get your training log to CVC for our records. If you are interested in further information regarding this trial, please contact Clinical Trial Project Lead, Courtney Gubbels at 1-800-707-9098 ext 2 or via email at courtney.gubbels@ualberta.ca or Regulatory Specialist Kalli Belseck, ext 6 or via email at kalli@ualberta.ca.

HEART-FID

We anticipate having our first Canadian sites activated in June with a first patient enrolled shortly afterwards. If you are interested in further information regarding this trial, please contact Clinical Trial Project Lead, Courtney Gubbels at 1-800-707-9098 ext 2 or via email at courtney.gubbels@ualberta.ca or Regulatory Specialist Kalli Belseck, ext 6 or via email at kalli@ualberta.ca.

We are proud to provide the visitors to our website with a more contemporary and comprehensive window into the CVC. In concert with our logo, we invite you to visit our new website: [CVC Website](www.thecvc.ca). This revitalized website is easily accessible, responsive, interactive, and informs users about who we are, our services, clinical research projects, and publications. We are proud to provide the visitors to our website with a more contemporary and comprehensive window into the CVC.

CVC Website

As always, we look forward to any comments or feedback you may have.

**HEART-FID**

Over the past 3 months we have really seen an increase in Canada’s enrollment with almost half of our patients being enrolled in the new year. Part of our sites success can be attributed to the Amendment 3 protocol enhancements but the majority of the success is due to sites diligently screening all their TAVR patients for possible trial inclusion.

We encourage our sites to keep up patient screening as the study is expected to complete enrollment in the summer. Site Study Reminders

- Amendment 3 also brought eCRF updates including the ‘Time of TAVR Procedure’ data point. The time entered should be the time the TAVR procedure is completed i.e. the time the closure device is placed at the end of the procedure.
- Please remember to record all endpoints within 24 hours of awareness and upload any source documents required to Box.
- In February our regulatory document focus was on ensuring your site had all training documents in place. If your site has completed as soon as possible and send a copy of your training log to CVC for our records.
- As a reminder please continue to send in your screening logs weekly to us.
- Data should be entered within 5 days of a visit. Please try to log in regularly to make sure that your site data is clean.

If you are interested in further information regarding this trial, please contact Clinical Trial Lead, Courtney Gubbels at 1-800-707-9098 ext 2 or via email at courtney.gubbels@ualberta.ca or Site Management Coordinator Paula Priest, ext 9 or via email at paula.priest@ualberta.ca.

**CVC Logo**

The Canadian VIGOUR Centre (CVC) is excited to announce the launch of our new visual identity. This transformation of the visual expression of our CVC “brand” was inspired by the CVC’s upcoming 20th anniversary and reflects both our proud history and bold future vision. A University of Alberta visual design class was challenged to come forward with an original concept and the leadership team unanimously selected the logo above created by Trevor Lau. Trevor’s logo evokes the shape of a heart, an image that is central to our organization’s objectives and identity. The heart is in turn formed by three distinct parts – the letters C, V and C.

The modern aesthetic of this design is a powerful visual that strongly communicates the CVC name and our evolving organizational identity. Additionally, the bridging between the letters is well aligned with our mission - Bridging hearts and minds to enhance cardiovascular care.

**CVC Website**

In concert with our logo, we invite you to visit our new website: [www.thecvc.ca](http://www.thecvc.ca). This revitalized website is easily accessible, responsive, interactive, and informs users about who we are, our services, clinical research projects, and publications. We are proud to provide the visitors to our website with a more contemporary and comprehensive window into the CVC.

As always, we look forward to any comments or feedback you may have.

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As always, we look forward to any comments or feedback you may have.
Lyndsey Garrity has very recently returned from a maternity leave and will be resuming her position as a Clinical Trials Project Lead within the CVC Operations group. Lyndsey will be assisting Courtney Gubbels on HEART-FID and then transitioning onto other projects in the near future. Lyndsey joined CVC in 2007 and is looking forward to connecting with everyone again, both at CVC and abroad. Lyndsey can be contacted at 780-492-3560 or by email lyndsey.garrity@ualberta.ca.

Did you know that, for the first time in over 20 years, the ICH-GCP guidelines for E6 have been updated? In November 2016 the ICH Assembly adopted ICH E6(R2). In their press release, it is noted this amendment “aims to encourage sponsors to implement improved oversight and management of clinical trials, while continuing to ensure protection of human subjects participating in trials and clinical trial data integrity. This amendment will now be implemented by ICH members through national and regional guidance”.

Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated. To download your copy of this guideline, please visit: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2/Step_4.pdf

Section 4.1.5 of ICH-GCP E6(R2) notes “The investigator should be designated a role in clinical trials of whom the investigator has delegated significant trial-related duties.” Commonly referred to as the “Site Signature and Delegation Log” by CVC. Your monitors will review this log during each visit, as well as collect a copy for the central file. It is essential that all staff who have a role in a clinical trial be designated as such on this log.

Each entry should note the person’s full name, their role, start/end dates, their initials and signature as well as an initial or signature of the PI to indicate their assent to this delegation.

This is a living document that should be updated continually during the life of the trial. If there are changes to a person’s role, the log should be updated accordingly, and the PI should initial/sign, and date, all changes to show agreement with the edits made.

Many logs do not have a place for the PI to date when they initial, so this may have to be added manually. Changes to the log without the PI’s updated initials/date is a common finding during monitoring visits/audits.

Another common issue with this log is that staff noted on the log are not qualified for a particular role that they have been assigned. For example, it is often noted by CRAs that Study Personnel, sites will be asked to amend the delegation log to delete this role from non-medical personnel.

Careful completion and maintenance of this log is an essential task during a clinical trial.

Lyndsey Garrity

Richard Rothery recently joined the CVC as an Academic Research Administrator. He received his BSc from Lancaster University in England, and a PhD in Biochemistry and Microbiology from the University of St. Andrews in Scotland. He moved to Edmonton and worked for many years as a Research Associate in the University of Alberta’s Department of Biochemistry, where he specialized in cryogenic electron paramagnetic resonance spectroscopy. Richard then joined the University of Alberta Grant Assist Program as a Project Coordinator, working on funding metrics and as a grant editor before moving to the CVC in December 2016.

Richard Rothery


Sandhu RK, Smigorsky M, Lockwood E, Savu A, Kaul P. Impact of Electrical Cardioversion on Quality of Life for the Canadian Cardiac Chronicle - Volume 21


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**Publication Information**

This newsletter is published periodically as a service to Canadian investigational sites. The purpose is to provide information of interest to individuals involved in cardiovascular clinical trials managed by the Canadian VIGOUR Centre, University of Alberta in Edmonton, Alberta, Canada.

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