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Composite Outcomes in Clinical Trials – What Happened to All-Cause Mortality as the Sole Endpoint?

Clinical trials, particularly in cardiovascular (CV) medicine, have improved the lives of patients in Canada and worldwide. As a consequence, a marked decline in mortality from CV disease in developed countries has made it increasingly challenging to demonstrate potential benefits of new, effective treatments when the primary outcome of a clinical trial is based on mortality alone. Thus, the era of large (e.g., n=42,000), simple (e.g., 4-page informed consent and 3-page case report forms) and efficient (e.g., 30-day follow-up post card given to patients surviving hospitalization to mail to the coordinating center) clinical trials like the first GUSTO study completed in 1993, have long since ended. Recognizing that surrogate outcomes may be misleading (recall the "suppress the premature ventricular complex PVC" approach that resulted in increased mortality with anti-arrhythmic therapies in the duet of CAST trials), clinical trial innovators like Califf, Topol, Braunwald, Cannon and others advocated for combining mortality with other nonfatal events to minimize the number of endpoints (and patients and time it would take) to evaluate new strategies and treatments.

However, as nicely discussed in a recent White Paper published in Circulation (2017;135:2299-2307) by our CVC Founding Director (Dr. Paul Armstrong) and Associate Director, Research & Strategic Planning (Dr. Cynthia Westerhout), despite the benefits in trial efficiency from combining events into a single composite outcome, "…this method assumes uniform directionality of each component, does not distinguish the relative clinical significance of each, and counts only the first occurrence of any event in the final tally within a conventional time to first event analysis." The most common current analytic approach assigns an equal "value" across all event types within the composite end point: thus, patients typically have a component of lesser severity than death as their first event conventional time to composite event analyses in trials. Further, unlike all-cause mortality, non-fatal events—even something like myocardial infarction (MI)—may be under-reported and are defined differently across studies.

In an attempt to address some of these limitations, Drs. Armstrong and Westerhout, in collaboration with Dr. Jeffrey Bakal (Lead, Health Research Methods and Analytics at the University of Alberta SPOR Data Platform) have proposed differentially weighting event types, with input from experienced trialists, clinicians, and patients themselves to derive a relative weighting system for individual patient outcome. They further point out that, even after differential weights within event types such as MI or stroke are accounted for, variability exists within each endpoint category with respect to clinical impact. For example, the clinical significance of an MI defined by a small troponin rise is likely different than a larger MI complicated by heart failure, and yet conventional analysis would "count" these two ends of the MI spectrum as being the same. Thus, additional attempts at grading the severity of individual end points within an event type--"weighting the weights"—may provide even greater discrimination between interventions that might not otherwise have been initially apparent.

Of note, the U.S. Food and Drug Administration (FDA) has recently chosen to restrict regulatory labeling of the recommended indication for empagliflozin in its label for diabetes to the reduction in CV death but not the primary composite of CV death, MI, or stroke. While both the former and the latter were statistically significantly lower with empagliflozin vs. placebo in the outcome-based EMPA-REG trial, MI and stroke were not. It will be

interesting to see how the FDA approaches potential recommended indications for another diabetes medication, once-weekly exenatide, that didn't quite achieve a statistically significant (p=0.06) for benefit in the recently presented EXSCEL trial. However, an almost 2% absolute reduction in the primary composite outcome (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke) was observed, together with a 1% absolute (14% relative [95% CI 0.77 to 0.97]) reduction in all-cause mortality.

Remarkably, since the study wasn't powered to definitively address all-cause mortality (and only CV death was included as part of the primary composite outcome), the observed death differences were "not considered to be statistically significant" on the basis of the pre-determined hierarchical testing plan. Yet, if you asked the many participating Canadian EXSCEL investigators, study coordinators, and their patients (in a trial very capably overseen by CVC project leads Courtney Gubbels, Karin Kushniruk, and Julianna Wozniak), they might consider the reduction in all-cause mortality to be a clinically important finding. Clearly we continue to face challenges in how composite end points are selected and how best to calibrate, analyze, and interpret their meaning and clinical relevance.

Shaun Goodman
CVC Co-director

SODIUM-HF

The SODIUM-HF study reached a major milestone this past summer. **Dr. Zieroth, Charissa, Wendy**, and **Jennifer** from St. Boniface Hospital in Winnipeg enrolled patient 400 into the study! This achievement was reached as a result of the cumulative efforts of all study coordinators, research assistants, dietitians, nurses, and principal investigators participating in this study. Thanks to everyone for your continued efforts to screen, enroll, and follow-up with patients. We look forward to seeing which site will be the one to break our next major milestone of 500 patients!

As of September 11, 2017, the SODIUM-HF study has over 400 patients randomized at 21 sites in Canada, Chile, Mexico, New Zealand, and Australia. We expect to activate additional sites from Canada, Australia, and Colombia in the fall.

Congratulations to the following sites for maintaining steady enrollment :

- **Dr. Porepa, Amir, and Jeanine** -Southlake Regional Hospital
- **Dr. Singh, Kristine, and Kelly** - Red Deer Regional Hospital
- **Dr. Troughton, Lorraine, and Helen** - Christchurch Heart Institute

General data queries and REDCap data queries were recently sent to all sites. As a reminder, please respond to all queries by the upcoming **data entry cut of September 30, 2017**. Please ensure that all completed study visits and phone calls have been entered and saved as complete (i.e., green) in REDCap by the data cut. If you are sending 3-Day Food Records or source documents, please ensure

that all documents will be received by the Core Lab (**sodcore@ualberta.ca**) before the upcoming deadline.

We will be sending out invitations soon for the fall **Dietitian/Study Coordinator Working Group Teleconference**, which will take place in October 2017. During this meeting, we will cover trial updates, enrollment, REDCap reminders, and study metrics. Keep your eyes out for the invitation! Minutes will be sent out shortly thereafter in the quarterly SODIUM-HF Newsletter.

If you are interested in receiving more 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**. You may also contact the SODIUM-HF trial Regulatory Specialist, Kate Dawson, at 780-492-3789 or via email at **kedawson@ualberta.ca**.

SODIUM-HF

Funded by the Canadian Institute of Health Research (CIHR), SODIUM-HF is a multicenter, randomized, open-label Study Of DIetary Intervention Under 100 MMOL in Heart Failure.

ClinicalTrials.gov Identifier: NCT02012179

GALILEO

With the summer break over and autumn upon us, we are rapidly approaching the enrollment target for GALILEO. We encourage all sites to screen and randomize as many patients as possible before the enrollment target is met. Be sure to include valve-in-valve patients when you are screening for GALILEO. We look forward to seeing more randomizations this fall and ending the trial on a high note in Canada!

Congratulations to our top enrolling sites:

- **Dr. Della Siega and Elizabeth Pelzer**, Victoria, BC – 10 patients
- **Dr. Horlick and Libo Wu**, Toronto, ON – 8 patients
- **Dr. Cantor and Kim Robbins**, Newmarket, ON – 7 patients
- **Dr. Toleva, Kiran Atwal, and James Ducas**, Winnipeg, MB – 7 patients

With regards to data, updated eCRF guidelines were sent to sites on July 12, 2017 along with an email which contained clarification on how to enter the time of administration of ASA if it is not taken on the same day as randomization. The guidelines also explain the process for signing CRF pages in Marvin, including Randomization and Medical History pages, something that data management is asking that sites now do for Screening/Baseline visits.

If your site's data is clean (i.e., query-free) and your monitor has reviewed these CRFs, then your site's PI or SC can begin the signing process – refer to section 4.2 in the guidelines for further details. Lastly, for patients who have stopped study drug permanently and have had an End of Treatment (EOT) visit, remember that subsequent visits must be added **manually** in Marvin since there is no longer a need to call into IXRS for these patients at each visit. These are called "Scheduled Visit (After EOT)" in Marvin.

The most recent Mass Communications listing was last sent to sites on July 20, 2017. Please ensure your site has printed and filed all study communications. Please let CVC know if you are missing any communication(s), and we will re-send the missing documents to you for filing. An updated listing will be sent to sites in October.

Key Reminders:

- After the monitor has performed **drug reconciliation**, study drug is to be destroyed on site per the site's SOP on Drug Destruction.
- **Visit 4** (Day 180) is a clinic visit in Canada.
- Please continue to send your **screening logs** weekly until the end of the enrollment period.
- Please review **patient contact information** at every visit to avoid any LTFU patients.
- Please remember to send in your **invoices** for any outstanding items per your site's contract/budget.

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

Sponsored by Bayer Healthcare AG, GALILEO is a Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes.

ClinicalTrials.gov Identifier: NCT02556203

HILO-HF

Congratulations to **Dr. Ezekowitz, Nariman, and Quentin** on their continued rapid enrollment of patients into the HILO-HF pilot study.

The team is nearly at the halfway point, with over 20 patients enrolled in the pilot study. They continue to demonstrate a strong commitment to enrolling patients into the HILO-HF Registry, with a total of 30 patients enrolled to date. Keep up the great work!

If you would like further information on the HILO-HF study, please contact the Clinical Trial Project Lead, Nubia Zepeda, at 1-800-707-9098 ext. 8 or via email at **nzepeda@ualberta.ca**.

Funded by the Heart and Stroke Foundation and Alberta Innovates Health Solutions, HILO-HF is a study examining High versus Low SpO2 Oxygen Therapy in Patients with Acute Heart Failure.

ClinicalTrials.gov Identifier: NCT02518828

ODYSSEY OUTCOMES

We are almost there! Follow-up in ODYSSEY Outcomes is just about complete and final visits will start soon. All CESD visits should now be booked. Please be sure to notify CVC of any new bookings that have been made, or if there are any changes to existing bookings.

Thank you for all of your efforts with patient retention! For those patients who are off study drug **temporarily**, the PI needs to decide whether the patient should resume study drug or **permanently** discontinue IP. Any patient who is temporarily off study drug and who has had their last regular clinic visit prior to the CSED should have their status changed to permanently off study drug in IXRS and RAVE, since they did not resume study drug at their last visit. Of course, they are expected - as are all randomized patients - to attend the Final Visit.

Central Lab kits for the Final Visits were sent to CVC sites in early September. Two types of kits were included in these shipments – those for "completers" and those for patients who discontinued study drug (permanently). The "discontinued study drug" lab kits are to be used for patients who discontinued study drug **more than 6 months before** the CSED. Please contact your Project Lead at CVC if you have any questions about these lab kits.

As expected, the turn-around time for data entry and submission of source documents for Endpoints (CEC) or SAEs (Safety/PV) will be very tight during this CSED period. The goal is for these activities to be done within **1 business day**. Remember that Safety (PV) and the CEC are two distinct groups for the ODYSSEY Outcomes trial. Please be sure to email/fax the required documents to the appropriate group.

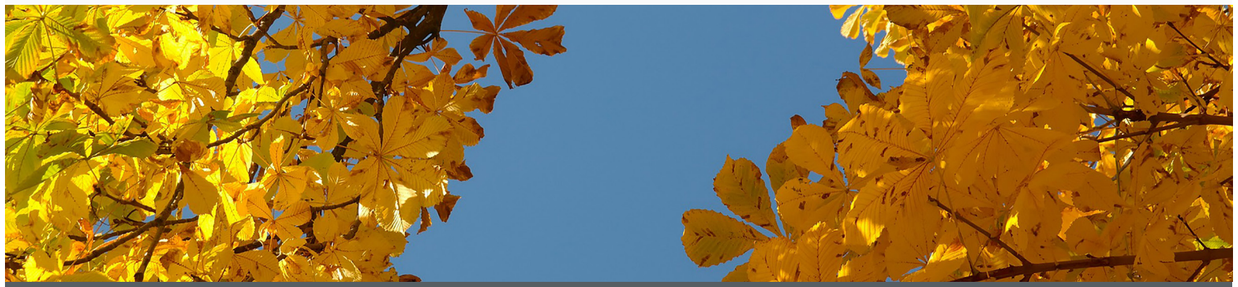
Lastly, please ensure patients have signed the last amendment ICF at the CSED visit if they have not already done so. Otherwise, please be sure to document your site's attempts to have the patient re-consented on this latest amendment and notify your REB per their reporting requirements.

If you have any questions about this trial, please contact Clinical Trial Project Lead, Julianna Wozniak at 1-800-707-9098 ext. 1 or by email at jwozniak@ualberta.ca.

Sponsored by Sanofi-aventis Recherche & Développement 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.

ODYSSEY OUTCOMES

ClinicalTrials.gov Identifier: NCT01663402



VICTORIA-HF Registry

We are excited to start the selection process for the VICTORIA-HF registry. If your site is participating in the VICTORIA trial, please keep an eye out for the feasibility questionnaire via email. We appreciate and look forward to your quick responses.

This registry will complement the VICTORIA randomized clinical trial and help us to further our understanding of heart failure. From the study, we hope to gain insight related to the baseline characteristics, practice patterns, and in-hospital outcomes of patients hospitalized for heart failure in North America. We expect to enroll up to 750 heart failure patients from approximately 15 Canadian sites throughout the duration of the study.

If you are a site participating in the VICTORIA study and are interested in receiving further information about the VICTORIA Heart Failure Registry, please contact the Clinical Trial Project Lead, Nubia Zepeda, at 1-800-707-9098 ext. 8 or via email at nzepeda@ualberta.ca. Regulatory Specialist, Kalli Belseck, may be reached by email at kalli@ualberta.ca.

VICTORIA-HF Registry

Sponsored by Merck and Bayer this registry will assess the risk/benefit profile of Vericiguat in those patients with chronic heart failure.

EXSCEL

With summer drawing to a close, so too are the final pieces of the EXSCEL trial.

We would like to thank everyone for all of your hard work to ensure the timely completion of the last required follow-up items for EXSCEL. The successful conclusion of this trial is a reflection of your continued effort and commitment to the study from start to finish!

If you have not done so already, please be sure to submit your site's **notice of study termination** to your REB as soon as possible before forwarding the relevant submission and acknowledgement reports to CVC. Thank you to the majority of sites that have already sent in these documents. Additionally, please inform CVC whether or not you intend to use the **patient letter template**, which was sent out to EXSCEL sites in August.

If your site will be using the template, it must be submitted to your REB for approval prior to distribution to patients. Please forward the associated REB submission and approval letters to CVC if your site has submitted or will be submitting the template for REB approval.

As document archival will occur shortly, now is a great time to do one last check at your site for any outstanding training, REB, or other documents. As a reminder, please refrain from archiving your site's documents until this has been authorized by the Sponsor.

The study's primary results were presented at the 53rd European Association for the Study of Diabetes meeting in Lisbon, Portugal on September 14, 2017. They were also published simultaneously in the New England Journal of Medicine entitled "***Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes*** [DOI: 10.1056/NEJMoa1612917]".

The trial met its primary safety objective of non-inferiority for MACE. The efficacy objective of a superior reduction in MACE did not reach statistical significance, although a prespecified analysis suggested all-cause mortality was lower with exenatide than placebo. "The study results show that exenatide had no adverse effects on cardiovascular

health, meaning that the drug could have an acceptable CV safety profile in people with type 2 diabetes who may have a wide range of existing cardiovascular conditions," said the DTU's Director Rury R. Holman, who co-led the study. "There did not seem to be any increase in the risk of hypoglycemia, acute pancreatitis, pancreatic cancer, or medullary thyroid carcinoma."

"It's encouraging for the field of diabetes to see these results in patients similar to what we see in clinical practice can have a potentially lower risk of death from all causes with the convenience of once-weekly dosing," said the DCRI's Adrian F. Hernandez, MD, MHS, Holman's co-leader on the trial. "This confirms the importance of carrying out large studies to evaluate impacts on cardiovascular outcomes. EXSCEL largely mirrored what we've learned from other studies of this class of medications - that they are safe and may have outcomes benefits."

Thank you for your continued dedication to the EXSCEL trial! Kate Dawson, the Regulatory Specialist supporting the archival and regulatory components of the EXSCEL trial at CVC, can be reached by phone at 780-492-3789 or by email at kedawson@ualberta.ca if you have any questions regarding these final study tasks. For further information regarding this trial, please contact Clinical Trial Project Lead, Julianna Wozniak, at 1-800-707-9098 ext. 1 or via email at jwozniak@ualberta.ca.

Sponsored by AstraZeneca, this trial is a pragmatic, long term, placebo- controlled, double-blinded trial which seeks to characterize the effects of exenatide once weekly on cardiovascular (CV) - related outcomes in patients with type 2 diabetes when added to the current usual care for glycemic control in a standard care setting.

EXSCEL Exenatide Study of Cardiovascular Event Lowering

ClinicalTrials.gov Identifier: NCT01144338

HEART-FID

Thank you to everyone who was able to attend the recent Investigator Meeting in Chicago. It was great to meet with all of you and see the overall eagerness for this trial!

Special congratulations to **Dr. Gordon Hoag** and **Robyn Standring** from Discovery Clinical Services in Victoria, BC for being the first activated site in Canada! We aim to have more sites activated very soon.

Please continue to complete the required regulatory documents and send them to CVC for review as quickly as possible. Additionally, please continue to follow up with your contracts department and Research Ethics Board to move your contract and ethics review along.

Other requirements for Site Activation:

- System access and training – RAVE EDC, ALMAC IXRS, CEC Box access
- Blinding Process Memo completion
- Site Initiation Visit (SIV)

Once your SIV has been **booked**, we will order your site supplies. You will receive your study binder, mini protocols, wallet cards, and Inclusion/Exclusion pamphlets. As well, you will receive your first order of lab kits for the central lab blood draws. The lab kits will be resupplied automatically after the first shipment.

After your SIV has been **completed** and there are no other outstanding items, your site will be activated and drug will be shipped within approximately 5 days.

When the study drug has been confirmed in the system, you will be ready to enroll your first patient! As you review patient charts, please contact us if you have any questions regarding the protocol inclusion/exclusion criteria.

We are eagerly awaiting the enrollment of our first Canadian patient.

If you are interested in receiving 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. Regulatory Specialist, Kalli Belseck, may be reached at 780-492-4011 or via email at kalli@ualberta.ca.

Sponsored by Luitpold Pharmaceuticals Inc., HEART-FID is a Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure With Iron Deficiency

HEART-FID

ClinicalTrials.gov Identifier: NCT03037931

STREAM-2

STREAM-2 is underway globally with the first patient recently enrolled in France.

We are excited for Canada to start contributing to the global enrollment later this year. Review of the trial is underway in Edmonton, AB, and trial logistic training pieces are in the process of being assembled.

As this is a unique collaboration between multiple health care teams, vigilant innovative personnel and streamlined procedures are necessary to ensure the success of the trial. Thank you to all of the groups involved for your efforts thus far.

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. Regulatory Specialist, Kalli Belseck, may be reached at 780-492-4011 or via email at kalli@ualberta.ca.

Sponsored by Leuven Research & Development (LRD) at University of Leuven, Belgium, STREAM-2 is a Phase 4 trial on STrategic Reperfusion in elderly patients Early After Myocardial Infarction

Stream-2 Strategic Reperfusion Early After Myocardial Infarction

ClinicalTrials.gov Identifier: NCT02777580

BEYOND 2000 (B2K)

It is a pleasure to announce the 23rd edition of the Beyond 2000 (B2K) symposium to be held Monday morning October 23rd in conjunction with the upcoming 2017 annual Canadian Cardiovascular Congress in Vancouver (http://beyond2000.org/). As is customary, our goal is to present a stellar educational event, and we look forward to welcoming back many of our Canadian colleagues. This year we will continue the binocular approach introduced in 2015 in order to provide attendees with diverse content tailored to their individual interests. Specifically, the overall B2K symposium will be comprised of two sequential sessions (see agenda inserts). Responding to prior feedback we have incorporated brief Q&A opportunities after each presentation using electronic media. Each session will also be enhanced by challenging case presentations directed towards key learning points.

In the first session, we'll explore the increasingly common and important subjects of **atrial fibrillation (AFib) and heart failure (HF)**. Recognized thought leaders will speak on new concepts and therapies for managing heart failure and contemporary treatment strategies in diabetic patients with heart failure. Thereafter, a spirited debate on whether old school therapies have a continuing role in the treatment of heart failure, sinus rhythm and left ventricular dysfunction. Finally, we will discuss the hot button issues in heart failure and atrial fibrillation.

The second session is aimed at our traditional target of **acute coronary syndromes (ACS)**. You can expect to be informed by key thought leaders on new ACS clinical trials in progress, as well as integrating new lessons learned from recent clinical trials into practice. The remarkable new options in secondary prevention with lipid modifying therapy will be explored; as well as a thoughtful discussion on aligning health care resources with ACS patient care needs in these modern times. We have planned another lively debate about the preferred therapy for secondary prevention post myocardial infarction is the traditional dual antiplatelet therapy or whether the new novel oral anti-thrombotics are preferred. A rapid fire summary of the hot button issues in ACS will conclude our symposium.

This year our symposium will be held in Vancouver, one of Canada's most beautiful cities, beginning at 0700 on October 23rd, 2017. We look forward to seeing you there and the opportunity to engage with our many friends, collaborators and colleagues in this exciting event.

Paul W. Armstrong, MD

Publications

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