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 endpoint: 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 endpoints 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% observed death differences were “not considered to be statistically significant” on their continued rapid enrollment of patients into the study.

Congratulations to our top enrolling sites:

- **Dr. Dela 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.

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!

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We are almost there! Follow-up in ODYSSEY Outcomes is just about complete and final visits will start soon. All CELD 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.

If your site is 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.

“Although we did not see any increase in the risk of hypoglycemia, acute pancreatitis, pancreatic cancer, or medullary thyroid carcinoma,” Holman continued. “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 DCRG’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 kadedawson@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 email at jwozniak@ualberta.ca.

ODYSSEY OUTCOMES

The Canadian Cardiac Chronicle

EXSCEL

The Canadian Cardiac Chronicle

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 Venesigat in those patients with chronic heart failure.

ClinicalTrials.gov Identifier: NCT01663402

EXSCEL

Sponsored by AstraZeneca, this trial is a pragmatic, long term, placebo-controlled, double-blind 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.

ClinicalTrials.gov Identifier: NCT01144338

ClinicalTrials.gov Identifier: NCT01663402

ClinicalTrials.gov Identifier: NCT01144338
STREAM-2

- 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, Kalil Belecky, may be reached at 780-492-4011 or via email at kalil@ualberta.ca.

**Sponsored by Latipool Pharmaceuticals Inc., HEART-FID is a Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Jotadurit (Ferrocyanide Carbamate) as Treatment for Heart Failure With Iron Deficiency**

**HEART-FID ClinicalTrials.gov Identifier: NCT03879931**

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 Standering 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

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**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 all of the group members for your efforts thus far.

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**B EYOND 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 provide 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 be 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 antplatelet therapy or whether the new novel oral anti-thrombics 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.

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Paul W. Armstrong, MD

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Publications Continued


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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