Title: DOuble SEquential External Defibrillation for Refractory VF- DOSE VF Randomized Control Trial

Version: 6.2 Dated: June 11 2021

Principal Investigator: Dr. Sheldon Cheskes, MD, CCFP (EM) FCFP

Title: DOuble **SE**quential External Defibrillation for Refractory **VF**- DOSE VF Randomized Control Trial

Structured Abstract:

Introduction: Despite significant advances in resuscitation efforts such as cardiopulmonary resuscitation (CPR) quality, defibrillation, airway management and antiarrhythmic medications given in hopes of promoting the return of an organized rhythm; there are some patients who remain in refractory ventricular fibrillation (VF) during out-of-hospital cardiac arrest. Double sequential external defibrillation (DSED) and vector change defibrillation (VC) have been proposed as a viable option for patients in refractory VF.

Objective: The objective of this study is to compare two novel therapeutic defibrillation strategies (DSED and VC) against standard practice for patients remaining in refractory VF during out-of-hospital cardiac arrest.

Research Question: Among adult (≥ 18 years) patients presenting in refractory VF or pulseless ventricular tachycardia (pVT) during out-of-hospital cardiac arrest, does DSED or VC defibrillation (anterior-posterior compared to anterior-lateral pad position) result in greater rates of survival to hospital discharge compared to standard defibrillation?

Methods: This will be a three-arm, cluster randomized trial with crossover conducted in six regions of Ontario, Canada (Peel, Halton, Toronto, Simcoe, London and Ottawa) over a three year period of time. According to randomized cluster assignment, all adult (≥ 18 years) patients presenting in refractory VF (defined as patients presenting in VF/pVT and remaining in VF/pVT after three consecutive standard defibrillation attempts each separated by 2 minutes of CPR) during out-of-hospital cardiac arrest of presumed cardiac etiology will be treated by one of three strategies: (1) continued resuscitation using standard defibrillation; (2) resuscitation involving DSED; or (3) resuscitation involving VC (change of defibrillation pads from anterior-lateral to an anterior-posterior pad position) defibrillation. The primary outcome will be survival to hospital discharge. Secondary outcomes will include neurologic outcome at hospital discharge, return of spontaneous circulation (ROSC), termination of VF after the first interventional shock, termination of VF inclusive of all interventional shocks, and number of defibrillation attempts to obtain ROSC. Based on our previous cohort study research and the DOSE VF pilot RCT, we will also perform an a priori subgroup analysis comparing rates of survival to hospital discharge for those randomized to DSED who receive DSED after three failed successive standard shocks (early DSED or first DSED shock is shock 4-6) to those who receive DSED after six failed successive standard shocks (late DSED or first DSED shock is shock 7 or later).

Impact: A well-designed randomized controlled trial employing a standardized approach to alternative defibrillation strategies early in the treatment of refractory VF is urgently required to determine if the treatments of VC defibrillation or DSED impact clinical outcomes.

Background:

Out-of-hospital cardiac arrest accounts for over 350,000 unexpected deaths each year in the United States and Canada, nearly 100,000 of which are specifically attributable to ventricular fibrillation or pulseless ventricular tachycardia (VF/VT).[1] VF/VT is considered the most treatment-responsive presentation of cardiac arrest and boasts the highest rate of survival. However, despite significant advances in resuscitation efforts such as CPR quality, defibrillation, airway management, and antiarrhythmic medications given in hopes of promoting the return of an organized rhythm, there are some VF patients who remain in persistent or refractory VF. The definition of refractory VF varies, but is commonly considered persistent VF without response to five standard defibrillation attempts.[2] Another common definition for refractory VF is those patients for whom VF is not terminated 5 seconds post defibrillatory shock and thereafter remain in VF.[3] From a pragmatic point of view, this definition would be difficult to apply to current cardiac arrest resuscitation practice. Shorter post-shock pauses induce CPR artifact making interpretation of VF termination 5 seconds post- shock problematic. As well, current resuscitation require 2 minutes of CPR without a pulse check following defibrillation making the determination of VF termination one that would not change clinical practice. It is important to note that refractory VF is different than recurrent VF, which is generally defined as VF that recurs after successful termination of a VF waveform.[4]

Double sequential external defibrillation (DSED) has been studied for decades in the electrophysiology lab for patients in both refractory atrial fibrillation and ventricular

fibrillation.[5-10] Recently, case series and individual case reports have surfaced demonstrating conflicting outcomes for patients treated with DSED for refractory VF, both in and outside the hospital.[11-16] Cabanas *et al*., were able to demonstrate improved termination of VF employing a prehospital protocol with use of DSED but reported no improvement in survival. This was likely due to late application of DSED (meant time to first DSED shock was 36.8 minutes, mean number of shocks prior to DSED was eight).[11] Ross *et al*., in a retrospective analysis of 50 DSED cases over a three year time frame, demonstrated no improvement in the primary outcome of neurologically intact survival employing DSED, but did not report data regarding the timing of the DSED shock nor CPR quality.[12] Lybeck *et al*., and Johnson *et al*., both described cases of early use of DSED with successful outcomes of neurologically intact survival to hospital discharge.[13,14] Despite growing enthusiasm, particularly in the field of prehospital medicine, there is a paucity of evidence to support widespread implementation of this therapy. Further, most uses of DSED have been employed as an ad-hoc final effort to convert VF, as opposed to a planned early application of this alternative treatment strategy. From a mechanistic viewpoint, it is unclear whether the change of vector, timing of the "dual shocks" or the application of increased energy is the curative factor for those responding to DSED. Our research group evaluated 251 cases of refractory VF (201 standard care, 50 DSED) over a three-year period beginning on Jan 1, 2015 in four Canadian EMS agencies currently participating in the DOSE VF pilot RCT. Our research demonstrated improved rates of VF termination and ROSC when comparing early DSED (shocks 4-8) to similar shocks provided by standard defibrillation. Specifically, when early defibrillation attempts were considered (defibrillation attempt 4-8), VF termination was higher for those receiving DSED compared to standard defibrillation (29.4% vs. 17.5%; RR: 1.7; 95% CI: 1.1 to 2.6). Additionally, when early defibrillation attempts were

considered (defibrillation attempt 4-8), ROSC was higher for those receiving DSED compared to standard defibrillation (15.7% vs. 5.4%; RR: 2.9; 95% CI: 1.4 to 5.9).

The DOSE-VF Pilot RCT

Based on our preliminary work, our research group obtained funding from the Laerdal Foundation to conduct an internal pilot trial of the DOSE VF protocol (https://clinicaltrials.gov/ct2/show/NCT03249948) previously approved by the Sunnybrook Health Sciences Center REB. The pilot trial was designed to determine the feasibility of conducting a full-scale randomized trial in this population.[17,18] The pilot RCT completed on September 9, 2019, trained over 2,500 paramedics in the technique of DSED and vector change defibrillation (VC). The pilot took place in four paramedic services in Ontario (Toronto, Peel, Halton and Simcoe) with all services actively enrolling patients. All paramedics received in-person training using a combination of didactic, video and simulated scenarios prior to the study launch. All eligible patients with refractory VF (n=152) in the participating paramedic services have had paramedics successfully apply both VC and DSED. The DOSE-VF Pilot RCT demonstrated that the protocol is feasible with 89.5% of patients receiving the treatment they were randomized to and 90.2% of patients receiving an intervention shock prior to shock 6 in the resuscitation. As well, no safety concerns were noted (no reports of defibrillator damage, skin burns, inadvertent shocking of paramedics or bystanders) and was well accepted by paramedics in the field. We have as well been able to determine the number of cases occurring in each service during the pilot RCT (varying from 1.4-6.1 cases/month) allowing us to accurately calculate the number of patients required to perform an adequately powered definitive RCT. Finally, we observed that the rate of VF termination and ROSC were greater in both

interventions then standard defibrillation. Specifically, in the standard group, 66.6% of cases resulted in VF termination, compared to 82.0% in VC and 76.3% in the DSED group. ROSC was achieved in 25.0%, 39.3% and 40.0% of standard, VC and DSED groups, respectively. The DOSE-VF pilot RCT has established the feasibility of proceeding with a definitive, adequately powered RCT to determine whether employing a standardized approach to alternative defibrillation strategies early in the treatment of refractory VF may impact clinical outcomes.

Objective: The objective of this study is to compare two novel therapeutic defibrillation strategies (DSED and VC) against standard practice for patients remaining in refractory VF during out-of-hospital cardiac arrest.

Research Question: Among adult (≥ 18 years) patients presenting in refractory VF or pulseless ventricular tachycardia (pVT) during out-of-hospital cardiac arrest, does DSED or VC defibrillation (anterior-posterior compared to anterior-lateral pad position) result in greater rates of survival to hospital discharge compared to standard defibrillation?

Population: Adult (≥ 18 years) patients presenting in refractory VF/pVT during out-of-hospital cardiac arrest. Refractory VF will be defined as patients in whom VF/pVT is the presenting rhythm and whom remain in VF/pVT after three successive failed defibrillation attempts each separated by 2 minutes of CPR.

Intervention: (1) Resuscitation involving DSED, or (2) Resuscitation involving VC defibrillation (anterior-lateral compared to anterior-posterior pad position).

Comparison: Resuscitation using standard defibrillation (pads in anterior-lateral position throughout the resuscitation).

Outcomes: The primary outcome will be survival to hospital discharge. Secondary outcomes will include neurologic outcome at hospital discharge, ROSC, termination of VF after the first interventional shock, termination of VF inclusive of all interventional shocks, and number of defibrillation attempts to obtain ROSC. We will also perform an a priori subgroup analysis comparing rates of survival to hospital discharge for those randomized to DSED who receive DSED after three failed successive standard shocks (early DSED or first DSED shock is shock 4-6) to those who receive DSED after six failed successive standard shocks (late DSED or first DSED shock is shock 7 or later). We will also perform a sensitivity analysis examining the effect of time period (pilot study, pre-COVID, during COVID) on our outcomes.

Inclusion Criteria: ≥18 years of age, non-traumatic cardiac arrest of presumed cardiac etiology, with a presenting rhythm of ventricular fibrillation/pVT; with no ROSC or non VF rhythm after three consecutive shocks.

Exclusion Criteria: Traumatic cardiac arrest, patients with pre-existing do not resuscitate orders, , patients in recurrent ventricular fibrillation (defined as those with a secondary presentation of VF (not the presenting rhythm) or those presenting in VF but did not receive three consecutive failed defibrillation attempts). Patient's whose initial care was provided by non-participating EMS agencies or fire services will be excluded.

Methods:

Study Design and Population

This will be a three-arm, cluster randomized trial with crossover conducted in six regions of Ontario, Canada (Peel, Halton, Toronto, Simcoe, London and Ottawa). These six regions were

selected because each has its own paramedic service, and all have previously participated in and successfully completed prehospital resuscitation trials.[19, 20] Two treatment strategies (DSED and VC) will be simultaneously assessed against a common control group (standard defibrillation). This approach has been chosen to maximize efficiency, allowing comparison of two new treatments to usual care in a single three-armed randomized trial.[21, 22]

The clusters will be defined by the paramedic service in each of the six regions and each cluster will crossover at least twice per year to receive one of three treatment approaches (standard care, DSED or VC) for six months. Each service will apply each of the three treatment arms twice over the duration of the study The annual prevalence of paramedic treated out-of-hospital cardiac arrest for these regions is approximately 4,000; of which 800 (20.0%) patients will present in VF. Our pilot trial suggests that approximately 180 patients per year will meet the study criteria for refractory VF. The study protocol will be approved by each local institutional Research Ethics Board and is registered with clinicaltrials.gov. (https://clinicaltrials.gov/ct2/show/NCT04080986).

All adult (≥ 18 years) patients remaining in refractory VF or pVT during out-of-hospital cardiac arrest of presumed cardiac etiology will be eligible for inclusion. Patients suffering a traumatic cardiac arrest, patients with pre-existing do not resuscitate orders and patients in recurrent ventricular fibrillation (defined as secondary presentation of VF or those presenting in VF but did not receive three consecutive defibrillation attempts) will be excluded. Patient's whose initial care was provided by non-participating EMS agencies or fire services will be excluded.

Study Protocol:

All paramedics treating patients during out-of-hospital cardiac arrest follow a provincial protocol for treatment of patients in VF **(Appendix 1)**. Cardiopulmonary resuscitation (CPR) will be performed prior to defibrillator pad application. Each rhythm analysis will occur at standard two-minute intervals. VF will be determined by paramedic manual defibrillator analysis or semi-automatic defibrillator analysis by participating fire services, after which a shock will be provided. For all patients, the first three shocks will occur with defibrillation pads placed in the anterior-lateral position. Epinephrine and antiarrhythmic medication (amiodarone or lidocaine) will be provided as per provincial protocol. For eligible patients remaining in VF after three consecutive shocks (following two-minute CPR intervals) that are delivered by paramedics or participating fire services (defibrillation shocks provided by bystanders prior to EMS arrival will not be counted), all subsequent defibrillations will be randomized to one of the following treatment strategies:

Strategy 1 **(Standard Defibrillation):** For paramedic services randomized to standard defibrillation, all subsequent defibrillation attempts will occur through pads placed in an anterior-lateral configuration as noted in **Appendix 1**.

Strategy 2 **(VC Defibrillation)**: For paramedic services randomized to VC defibrillation, all subsequent shocks will be delivered using anterior-posterior pad placement, as noted in Appendix 1. Transfer of pads to the anterior-posterior position from the initial standard anterior-lateral configuration will occur during the two-minute cycle of CPR following the third shock with minimal interruptions in CPR.

Strategy 3 **(DSED)**: For paramedic services randomized to DSED, paramedics will apply a second set of defibrillation pads as soon as possible after the first three shocks (via a second

paramedic or fire defibrillator) in the anterior-posterior position, as noted in **Appendix 1**. Application of defibrillation pads for the second defibrillator will occur during the two-minute cycle of CPR following the third shock with minimal interruptions in CPR. All subsequent defibrillation attempts will be carried out by sequential defibrillation shocks provided by two defibrillators. To ensure shocks are not applied at the exact same moment, we will employ a short (less than one second) delay to provision of the second defibrillator shock. This will be accomplished by a single paramedic pressing the "shock button" on each defibrillator in rapid sequence as opposed to simultaneously. Dispatch deployment strategies will be employed by all paramedic services participating in the trial to ensure two defibrillators are available for all cardiac arrests in the DSED arm of the study. However, in situations when a second defibrillator is not available, the treatment will default to standard defibrillation until such time that a second defibrillator can be secured.

Randomization Strategy

Each cluster (paramedic service) will be randomized to standard defibrillation, defibrillation using VC, or DSED (see attached timeline in **Appendix 2**). All clusters will crossover between standard defibrillation, defibrillation using VC or DSED at least twice per year (at least six distinct treatment periods). Random assignment of treatment sequence will be performed by the coordinating center prior to the start of the study. Specifically, each paramedic agency will perform each arm of the study twice during the duration of the trial. Clusters will not be informed of their group assignments until necessary to make preparations to start the trial or crossover to another study strategy.

Outcome Measures

The primary outcome will be survival to hospital discharge. Secondary outcomes will include neurologic outcome at hospital discharge, ROSC, termination of VF after the first interventional shock, termination of VF inclusive of all interventional shocks, and number of defibrillation attempts to obtain ROSC.

Sample Size

In response to the need for more efficient trial designs that accelerate discovery and minimize costs, it has been recommend that researchers consider employing multi-arm trials designed for logistical efficiency.[21] In a multi-arm trial, several treatments are simultaneously assessed against a common control group within a single randomized trial, allowing sizeable gains in efficiency. Relative to conducting separate trials for each experimental treatment, a multi-arm design has been shown to require a lower total sample size and financial resources than separate, sequential two-arm trials.[22]

From our internal pilot trial discussed earlier, we observed that across our paramedic services, the annual prevalence of paramedic treated out-of-hospital cardiac arrest for these regions is approximately 4,000; of which 800 (20.0%) patients will present in VF. Our pilot data suggests that approximately 180 patients per year meet the study criteria for refractory VF. Holmen et al.[24] demonstrated a 30 day survival rate of 28.7% for patients receiving 1-3 shocks, declining to 12.4% for those receiving 4-10 shocks, and 4.9% for those receiving greater than 10 shocks. Based on these findings, we assumed a baseline survival rate of 12% for patients who will meet our study criteria. This baseline survival rate will be confirmed by comparing to the baseline survival rate of the standard defibrillation arm of the pilot RCT and will be adjusted according to this value.

We hypothesize that DSED and VC defibrillation earlier in the resuscitation will result in survival as high (or higher) as standard defibrillation. We project a minimum absolute increase of 8% in survival to hospital discharge when VC or DSED strategies are employed as per our protocol, compared to standard care.

Using these baseline estimates, and assuming a fixed number of paramedic service clusters (n=6), we will enroll approximately 20-70 patients per cluster over one year. Data from the internal pilot RCT will be included in the final analysis.[17] The study design assumes that each cluster will cross over twice to receive each of three treatment approaches (standard defibrillation, DSED and VC) for approximately six months. We assumed a plausible intra-cluster correlation (rho) of 0.010 and a plausible inter-period correlation (eta) of between 0.008 and 0.010 and without multiplicity correction, as has been recommended for exploratory trials involving multiple treatment arms.[22,25] Under these conditions, the trial will have adequate power (>80%) with an α level 5%, to detect a minimally important 8% absolute difference in survival to hospital discharge with a sample size of 310 patients per arm (total sample size of 930 patients; approximately 150 patients from internal pilot RCT and 780 patients from the definitive RCT).

Statistical Analysis and Mock Tables **(Appendix 3**):

For this three-arm trial, two treatment strategies (DSED and VC) share a common control arm (standard defibrillation). This approach is chosen to maximize efficiency, allowing comparison of two new treatments to usual care in a single three-armed trial. The primary analysis will compare DSED to standard defibrillation and VC defibrillation to standard defibrillation. A secondary analysis will compare DSED to VC defibrillation. We hypothesize

that resuscitation involving DSED and resuscitation involving VC defibrillation will have superior outcomes compared to resuscitation using standard defibrillation. Because this trial is focused on answering the efficacy question for each treatment strategy separately, and the interpretation of the results of one comparison have no direct bearing on the interpretation of the other. In this situation, no multiplicity adjustment is required.[22, 25, 26]

All tests will be 2-sided with $p < 0.05$ denoting statistical significance. The unit of analysis for the comparisons will be the individual patient. All patients will be analyzed according to randomized treatment assignment (intention-to-treat analysis). Based on the DOSE VF pilot RCT secondary analyses will be performed based on actual treatment received, appropriate randomization performed, and appropriate randomization performed with optimal intervention shock timing (shock 4). We will also perform an a priori subgroup analysis comparing rates of survival to hospital discharge for those randomized to DSED who receive DSED after three failed successive standard shocks (early DSED or first DSED shock is shock 4-6) to those who receive DSED after six failed successive standard shocks (late DSED or first DSED shock is shock 7 or later). Last, we will perform a sensitivity analysis to examine the impact of trial phase (pilot study, pre-COVID, and during COVID) on our outcomes. The binary primary outcome, survival to hospital discharge, will be compared across the arms of DSED and VC defibrillation as an adjusted odds ratio with 95% confidence intervals (CIs) using the standard arm as the reference group.[27] We will use a generalized linear mixed model (GLMM; logit link) with random effects for cluster-period effect, and using fixed-effects for cluster and for the period, to account for the effect of period on the outcome, as has been recommended for the analysis of cluster crossover trials.[28,29] The primary analysis will also adjust for the following baseline variables known to impact outcomes after out-of-hospital cardiac arrest: age, sex,

bystander witnessed arrest, bystander CPR provided, time to first arrival, public versus private location, epinephrine and antiarrhythmic use.[30] We will also test for effect modification by trial phase, comparing effectiveness in the internal pilot trial and the larger definitive trial. Odds ratios with 95% CIs for secondary outcomes will be calculated in a similar manner, where appropriate.

Consent Waiver

This trial requires timely implementation of the study intervention, and individual patient consent will not be feasible prior to randomization. Similar to our previous research, we have received a waiver of consent in accordance with the Tri-Council Agreement from the Research Ethics Board of Sunnybrook Health Sciences Centre.[31-39] We will seek a similar waiver of consent from REB providing oversight to the EMS agencies taking part in the study. All enrolled patients will receive a letter notifying they were enrolled in the study under waiver of consent.

Data Collection

The Sunnybrook Health Sciences Centre in conjunction with the Sunnybrook Osler Centre for Prehospital Medicine will oversee data collection, management and data analyses. Data sources will include ambulance call reports (ACRs) and electronic defibrillator files that are mandatorily recorded and stored for each patient. Paramedic providers in participating regions will collect basic demographic information and details about the cardiac arrest, including adverse/critical events during transport in addition to other information concerning patient care. All services will also capture electronic defibrillator CPR process data, including real-time measures of chest compression fraction, compression depth (not available on all defibrillators),

compression rate and shock pause duration. These data collection processes were successfully implemented and tested in the pilot study. For each case identified as an eligible DOSE VF study data (listed below) will be abstracted by a data abstractor hired and trained for the study. Data will be abstracted from ACRs and electronic defibrillator files at Sunnybrook Centre for Prehospital Medicine, where the data are housed on a secure server. Cases from all agencies will be assigned a unique Study ID and all identifiers removed. Separate lists of ACR identifiers corresponding to the unique Study IDs will be maintained in a separate location.

All data will be handled according to national privacy legislation and its related regulations. Data will be entered into a standardized Epi Info 7 data collection form (Epi Info, Centers for Disease Control and Prevention, Atlanta, GA.) Data will be checked, validated, encrypted, and sent securely to Sunnybrook Health Sciences Centre for analyses.

Data to be abstracted from Ambulance Call Report and Electronic Defibrillator Files (Participating Fire Services or EMS):

General Characteristics: Study ID, Emergency health service, Fire service if applicable, age, sex, weight (approximate), arrest location (public/private), response time, bystander CPR, bystander AED, bystander shock, bystander witnessed, highest service level on scene (ALS vs BLS).

General Date/Time Information: Date of Call, call arrival to 911, arrival at scene (wheels stop 1st vehicle), arrival at patient side, time of first rhythm, second, etc. (all shocks), first shock, second shock, etc.(all shocks), depart scene, arrival at hospital.

Prehospital Treatment Data: Arrest occurred after EMS arrival (witnessed EMS), AED/Defib applied, total shocks delivered, number of each shocks (standard, vector change, DSED), time of first ROSC post arrest (ROSC will be defined as the restoration of a spontaneous rhythm noted on the defibrillator files with a corresponding palpable pulse noted on the paramedic ambulance call report) and termination of VF (defined as the absence of a shockable rhythm 2 minutes after each interventional or standard shock).

CPR quality characteristics: Median CCF during resuscitation, median compression rate during resuscitation, median compression depth during resuscitation.

Specific shock variables (for each shock): Pre-shock pause, post-shock pause, number of interventional or standard shocks that resulted in ROSC, rate of re-arrest post-ROSC.

Variables to be abstracted from a combination of electronic defibrillator files and the ACR

The data abstractor will use a combination of both electronic defibrillator files and the ACR to determine VF termination, time of first ROSC, as well as the number of defibrillatory shocks provided to first ROSC. All defibrillator files will be reviewed by two independent investigators blinded to the intervention to confirm VF termination as well as the subset of cases that meet the criteria for our subgroup analysis. Adjudication by a third investigator blinded to the intervention will occur should consensus be required.

Data linkage to administrative data bases at Cancer Care Ontario CCO:

The primary outcome of survival to hospital discharge will be obtained through linkage of our data with the administrative databases at Cancer Care Ontario (CCO). In addition we plan on collecting data regarding whether or not a patient had coronary angiography and/or

percutaneous coronary intervention (PCI). (ICD-10 codes (PCI): 4802, 4803, 1IJ50, 1IJ54, 1IJ57GQ and ICD-10 codes (angiography): 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4995, 4996, 4997, 3IP10). We expect this will occur within six months of the final patient enrolled. Patients who are discharged alive or transferred to a receiving hospital in Ontario and subsequently discharged alive, health card numbers and other patient information as necessary will be linked at CCO with the province-wide hospital discharge abstract database (DAD). (Linkage to the CCO administrative database requires use of the Ontario health card number for deterministic linking of each subject. Where no match is found, patient names and dates of birth will be used to search for corresponding records using probabilistic matching.)

On the recommendation of the DSMB we have decided to collect data on neurologic outcome as a secondary outcome for this study. We will obtain neurologic outcome in two different ways. First, we will link patient records with administrative databases at Cancer Care Ontario using the same method as we did for our primary outcome of survival to hospital discharge (described above). We will link patients to obtain "discharge disposition" from the Discharge Abstract Database (DAD) as a surrogate for neurologic status at hospital discharge. This has been done in previous cardiac arrest research to represent patient neurologic status. Second, we will obtain discharge summaries for patients who survived to hospital discharge by applying to Clinical Trials Ontario (CTO) for research ethics board approval to obtain data from participating hospitals. Neurologic status at hospital discharge will be obtained from discharge summaries by manual data abstraction through use of research assistants or hospital research personnel.

Trial Organization:

Coordinating Center

This study will be conducted coordinated through Sunnybrook Centre for Prehospital Medicine in Toronto who will provide oversight throughout the study including all interactions with participating EMS services. Statistical support will be provided through Sunnybrook Health Sciences Centre.

Steering Committee

The Executive Steering Committee will consist of a group of key scientific and local leaders and will oversee all aspects of the study. An EMS Operations Committee will be established and meet on a monthly basis to address the day-to-day operations of the trial.

Data and Safety Monitoring Board

Independent oversight of this study will be provided by a data safety monitoring board (DSMB) consisting of a biostatistician and two clinical experts, unrelated to the trial. The committee will conduct an unblinded interim data safety analysis to assess for lower than anticipated rates of survival between the three treatment groups. The committee will meet at one-year intervals and provide recommendations to the steering committee; however, the responsibility for the final decision regarding a DSMB-recommended course of action will rest with the steering committee.

Once 450 patients have been enrolled in the trial (including patients enrolled during the internal pilot trial), the DSMB committee will conduct an unblinded interim data analysis and will advise if sample size modification if necessary. Sample size modification based on unblinded interim results is relatively well understood and is unlikely to introduce bias or raise major concerns.[40-42] Depending on the estimates of the event rate, they may suggest we maintain

the a priori calculated sample size or increase it (but not decrease it). If a sample size increase is warranted due to lower than anticipated event rates, REB approval will be sought from each participating site.

During our interim analysis we will also formally examine stopping the trial for harm only. The decision to stop for harm will be based on a single interim analysis performed after 50% recruitment (n=450). We will use a Haybittle-Peto one-sided P value < 0.0005 as evidence of harm and criteria to stop the trial. This will not impact the alpha for our final analysis.[43] We will also monitor adverse events as they occur and take these into consideration during the interim analysis. The decision to stop the trial will be based upon recommendations by the DSMB in discussion with the trial steering committee.

Feasibility and Possible Problems

Recruitment and rates of patients presenting in refractory VF are based on local, historical data and the internal pilot RCT. Actual rates of refractory VF in the full trial may be higher or lower than projected which may impact the duration of study estimates. Enthusiasm for recruitment will be maintained with monthly updates to the paramedics and paramedic services through the activities of the EMS operations committee. The assurance of two defibrillators being available for all patients randomized to the DSED strategy has the potential to impact enrollment in this study arm but will be mitigated by changes in regional dispatch deployment in each region to assure two paramedic crews are dispatched to all cardiac arrest calls. Should one of the two intervention arms appear to be more successful than standard care, a risk of contamination of the study arm may exist for patients randomized to a perceived inferior treatment. This will be mitigated by education during the training of all paramedics on the

importance of maintaining randomization during the study, stickers applied to each service defibrillator labeled to the intervention arm as well as reminders of the importance of randomization to the validity of the study while the study is ongoing through continual education, individual and service wide paramedic feedback. Previous experience of our services in randomized controlled trials will also aid to guard against this occurrence. Defibrillation as currently proposed is Health Canada approved for both standard and VC arms of our study. We have received input from Health Canada that DSED as proposed in the study protocol is an off label use of defibrillation and its use is not within the purview of Health Canada, but does require the judgment of the local REB. We have obtained REB approval for the DOSE VF pilot from Sunnybrook Health Science Center.

Ethical and Regulatory Standards

Good Clinical Practice

The study will be conducted in accordance with both the Tri-Council Policy Statement[44] and Good Clinical Practice Guidelines.[45]

Approval of the Study Protocol

Before the start of the study, the study protocol and other appropriate documents must be submitted to and approved by the local institutional Research Ethics Board and the appropriate regulatory authorities in accordance with local legal requirements. Documentation of Ethics Committee/REB approvals and confirmation of executed institutional data sharing agreements will be required before study randomization and enrollment begin. The study protocol will be registered with clinicaltrials.gov.

Maintenance of Records

The Principal Investigator/Coordinating Centre must maintain all study records, patient files and other source data for up to 25 years as per institutional standard operating procedures.

Confidentiality

All personal health information will be kept confidential. Direct identifiers (e.g. name, date of birth) corresponding to each unique Study ID will be stored separately and securely at Sunnybrook Centre for Prehospital Medicine. Data will be de-identified using methods described by the Information and Privacy Commissioner of Ontario's De-identification Guidelines for Structured Data. The Principal Investigator agrees to maintain the confidentiality of the study protocol.

Confidentiality Agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigators (or any company acting on their behalf), inclusive of this protocol and the patient case report forms are the exclusive property of the Coordinating Centre. They may not be given or disclosed by the Investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of the Coordinating Centre. It is specified that the submission of this protocol and other necessary documentation to the Ethics Research Committee is expressly permitted, the Ethics Committee members having the same obligation of confidentiality. The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of

confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

Study Team	**Role**	**Affiliation**
Dr. Sheldon Cheskes	PI	Sunnybrook Centre for Prehospital Medicine
Dr. Richard Verbeek	Co-I	Sunnybrook Centre for Prehospital Medicine
Dr. Ian Drennan	Program Manager	Sunnybrook Research Institute
Dr. Shelley McLeod	Co-I	Sinai Health System
Dr. Ruxandra Pinto	Statistician	Sunnybrook Health Science Centre
Dr. Linda Turner	Statistician / Epidemiologist	Sunnybrook Centre for Prehospital Medicine
Dana Bradshaw	Data abstractor	Sunnybrook Centre for Prehospital Medicine
Dr. Michael Feldman	Co-I	Sunnybrook Centre for Prehospital Medicine
Dr. Matthew Davis	Co-I	London Health Science Centre

Dr. Damon Scales	Co-I	Sunnybrook Centre for Prehospital Medicine

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update. Circulation. 2014;129:e28–e292.

2. Slovis CM, Wrenn KD. The technique of reversing ventricular fibrillation: improve the odds of success with this five-phase approach. J Crit Illn. 1994 Sep;9(9):873–89.

3. Weaver WD, Cobb LA, Copass MK, Hallstrom AP. Ventricular defibrillation: a comparative trial using 175-J and 320-J shocks. N Engl J Med 1982;307:1101-6.

4. Van Alem AP, Post J, Koster RW, VF Recurrence: Characteristics and Patient Outcome in Out-of-Hospital Cardiac Arrest. Resuscitation 2003;59:181-188.

5. Pagan-Carlo LA, Allan .ll Spencer Kr, Birkett CL, Myers R, Kerber RE. Encircling overlapping multipulse shock waveforms for transthoracic defibrillation. Am CoIl Cardiol 1998:32:2065-2070 .

6. Kerber RE, Martins B, Kienzle MG, et al. Energy, current, and success in defibrillation and cardioversion: clinical studies using an automated impedance-based method of energy adjustment. Circulation 1988;77:1038-46.

7. Hoch DH, Batsford WP, Greenberg SM, et al. Double sequential external shocks for refractory ventricular fibrillation.] Am Coll Cardiol 1994:23:1141-5.

8. Gerstein NS, Shah MB, Jorgensen KM. Simultaneous use of two defibrillators for the conversion of refractory ventricular fibrillation. Cardiothorac Vasc Anesth 2015;29:421-4.

9. Alaeddini, J., Feng, Z., Feghali, G., Dufrene, S., Davison, N.H., Abi-Samra, F.M. Repeated dual external direct cardioversions using two simultaneous 360-J shocks for refractory atrial fibrillation are safe and effective. Pacing Clin Electrophysiol. 2005;28:3–7.

10. Marrouche, N.F., Bardy, G.H., Frielitz, H.J., Gunther, J., Brachmann, J. Quadruple pads approach for external cardioversion of atrial fibrillation. Pacing Clin Electrophysiol. 2001;24:1321–1324.

11. Cabanas JG, Myers J, Williams G, De Maio V, Bachman MW. Double sequential external defibrillation in out-of-hospital refractory ventricular fibrillation: a report often cases. Prehosp Emerg Care 2015;19:126-30.

12. Ross EM, Redman TT, Harper SA, Mapp JG, Wampler DA, Miramontes DA. Dual defibrillation in out-of-hospital cardiac arrest: A retrospective cohort analysis. Resuscitation 2016;106:14-17.

13. Lybeck AM, Moy HP, Tan DK. Double sequential defibrillation for refractory ventricular fibrillation: a case report. Prehosp Emerg Care 2015;19:554-7.

14. Johnston M, Cheskes S, Ross G, Verbeek PR. Double sequential external defibrillation and survival from out-of-hospital cardiac arrest: a case report. Prehosp Emerg Care 2016:1-5.

15. Leacock BW. Double simultaneous defibrillators for refractory ventricular fibrillation. Emerg Med 2014;46:472-4.

16. Cortez E, Krebs W, Davis], Keseg DP, Panchal AR. Use of double sequential external defibrillation for refractory ventricular fibrillation during out-of-hospital cardiac arrest. Resuscitation 2016;108:82-86.

17. Eldridge et al. Pilot and Feasibility Studies (2016) 2:64 DOI 10.1186/s40814-016-0105-8

18. Avery KNL, et al. BMJ Open 2017;7:e013537. doi:10.1136/bmjopen-2016-013537

19. Nichol G, Leroux B, Wang H et al. Trial of Continuous or Interrupted Chest Compressions during CPR. N Engl J Med 2015;373:2203-2214.

20. Kudenchuk PJ, Brown SP, Daya M et al. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. N Engl J Med 2016;374:1711-1722.

21. Parmar MK, Carpenter J, Sydes MR. More multi-arm randomised trials of superiority are needed. Lancet 2014; 384(9940):283-284.

22. Freidlin B, Korn EL, Gray R, Martin A. Multi-arm clinical trials of new agents: some design considerations. Clin Cancer Res. 2008;14(14):4368-71.

23. Scales DC, Cheskes S, Verbeek PR et al. Prehospital cooling to improve successful targeted temperature management after cardiac arrest: A randomized controlled trial. Resuscitation 2017;121:187-194.

24. Holmén J, Hollenberg J, Claesson, A, et al. Survival in ventricular fibrillation with emphasis on the number of defibrillations in relation to other factors at resuscitation. Resuscitation. 2017;113: 33-38.

25. Wason JM, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? Trials 2014;15:364.

26. Cook RJ, Farewell VT. Multiplicity considerations in the design and analysis of clinical trials. J R Stat Soc Ser A 1996;159:93–110.

27. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp clin trials 2007;28(2):182-91.

28. Murray DM, Varnell SP, Blitsyein JL. Design and analysis of group-randomized trials: A review of recent methodological developments. Am J Public Health. 2004;94(3):423-432.

29. Turner RM, White IR, Croudace T, et al. Analysis of cluster randomized cross-over trial data: a comparison of methods. Stat Med 2007;26(2):274-89.

30. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63(3):233-49.

31. Morrison LJ, Long J, Vermeulen M, et al. A randomized controlled feasibility trial comparing safety and effectiveness of prehospital pacing versus conventional treatment: 'PrePACE'. Resuscitation 2008;76:341-349.

32. Morrison LJ, Rizoli SB, Schwartz B et al. The Toronto prehospital hypertonic resuscitationhead injury and multi organ dysfunction trial (TOPHR HIT)--methods and data collection tools. Trials 2009;10:105.

33. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-890.

34. Aufderheide TP, Kudenchuk PJ, Hedges JR, et al. Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 1: rationale and methodology for the impedance threshold device (ITD) protocol. Resuscitation 2008;78:179-185.

35. Stiell IG, Callaway C, Davis D, et al. Resuscitation Outcomes Consortium (ROC) PRIMED cardiac arrest trial methods part 2: rationale and methodology for "Analyze Later vs. Analyze Early" protocol. Resuscitation 2008;78:186-195.

36. Morrison LJ, Dorian P, Long J, et al. Out-of-hospital cardiac arrest rectilinear biphasic to monophasic damped sine defibrillation waveforms with advanced life support intervention trial (ORBIT). Resuscitation 2005;66:149-157.

37. Morrison LJ, Nichol G, Rea TD, et al. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. Resuscitation 2008;78:161-169.

38. Newgard CD, Sears GK, Rea TD, et al. The Resuscitation Outcomes Consortium Epistry-Trauma: design, development, and implementation of a North American epidemiologic prehospital trauma registry. Resuscitation 2008;78:170-178.

39. Idris AH, Becker LB, Ornato JP, et al. Utstein-style guidelines for uniform reporting of laboratory CPR research. A statement for healthcare professionals from a Task Force of the American Heart Association, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine. Resuscitation 1996;33:69-84.

40. Chin R. Adaptive and Flexible Clinical Trials. Chapman and Hall/CRC Press, Taylor and Francis, New York, NY; 2012.

41. US Food and Drug Administration. 2010. Draft guidance for industry: adaptive design clinical trials for drugs and biologics. Available at:

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. Last accessed August 2, 2018.

42. Chang M, Chow SC, Pong A. Adaptive Design in Clinical Research: Issues, Opportunities, and Recommendations. J Biopharm Stat 2006;16(3):299-309.

43. Schulz KF, Grimes DA. Multiplicity in randomized trials II: subgroup and interim analyses. Lancet. 2005; 365: 1657-1661.

44. Canadian Institutes of Health, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada.

Tri-council policy statement: ethical conduct for research involving humans 2006.

Available: http://www.pre.ethics.gc.ca/english/policystatement/goals.cfm.

45. Health Canada. International Conference on Harmonization of Technical

Requirements for the Registration of Pharmaceuticals for Human Use Guidance E6: Good Clinical Practice: Revised Consolidated Guideline 2004.

Penn Medicine
Hospital of the University of Pennsylvania
Department of Emergency Medicine

Benjamin S. Abella, MD MPhil FACEP
Professor and Vice Chair for Research
Director, Center for Resuscitation Science

Dr. Sheldon Cheskes
Principal Investigator
Double Sequential External Defibrillation for Refractory VF – DOSE VF Study

January 28, 2022

Re: Data Safety Monitoring Board Review of Double Sequential External Defibrillation for Refractory Ventricular Fibrillation (DOSE VF) Randomized Controlled Trial.

On Friday January 28th 2022, the DSMB met virtually via Zoom to discuss the current status of the DOSE-VF RCT. Prior to the meeting, Dr. Sheldon Cheskes circulated a summary report detailing the current status of the DOSE-VF trial, which was reviewed by DSMB members Dr. Jim Christenson, Dr. Ben Abella, and Dr. Gerald Lebovic. Steering committee members Dr. McLeod, Dr. Verbeek, and Dr. Scales also attended the DSMB meeting to provide context and input regarding current challenges. This letter is intended to summarize the discussion from the DSMB meeting.

After a long pause due to the COVID-19 global pandemic, five sites restarted enrolment in September 2020. The sixth site, Toronto Paramedic Service, began enrolling patients again in October 2021 (after a 19-month hiatus). Since restarting the trial, 132 patients have been enrolled, bringing the total study enrolment to 379 with good balance between all arms (DSED 122; Standard 128; Vector Change 129 patients). Despite the continued enrolment of patients, Dr. Cheskes presented some concerns regarding the ability of paramedics to continue to enrol patients in the study due to the challenges presented by the ongoing COVID-19 pandemic. Some of the major concerns relate to paramedic protocol compliance during COVID-19; paramedic staffing concerns and service response times; and the reported worldwide decrease in overall survival from cardiac arrest (primary outcome of the study) during COVID-19.

Dr. Cheskes reported an overall decrease in randomization compliance during COVID-19 from 92% (pre-COVID) to 83% (during COVID), with compliance dropping in both intervention arms to 73% (down from 83% for vector change and 92% for DSED prior to the pandemic) with no significant drop in standard arm compliance. This is concerning as it has the potential to bias the trial results towards the null effect. The investigators have followed up with letters, video refreshers, sign postage at all stations and other methods in an attempt to keep compliance high, but feedback from paramedic services suggests compliance is difficult due to reduced staffing, increased response times, and competing priorities associated with COVID-19 protocols on scene and cardiac arrest treatment.

Dr. Cheskes reported a major increase in the number of patients that are receiving initial defibrillation from the fire department – from 32% pre-COVID to 39% during COVID (up to 53% in the largest centres - Toronto, Ottawa, and Peel). In some cases, patients are receiving multiple shocks (upwards of five) prior to paramedic arrival. This again speaks to reduced paramedic staffing levels, increased responses times, and reduced overall protocol compliance – again all potentially impacting the study findings. The critical component of the study protocol is to ensure early intervention shocks (vector change or DSED) after three failed standard shocks. The current pandemic creates a scenario whereby intervention shocks are being delivered at the 6th or later shock, impacting any potential benefit of the intervention again biasing the results towards the null effect.

Perhaps most difficult at this time is the impact of paramedic fatigue. Amazingly, Dr. Cheskes and his EMS operations committee have been able to maintain paramedic and service interest with this study during COVID-19 when many other trials have stopped. The paramedics have continued to enrol to the best of their ability but reduced staffing, increased call volume, and pandemic-related job stressors have caused significant burnout and fatigue within paramedic

services. Each service has spent a minimum of 18 months (except Ottawa Paramedic Service) and up to 3 years enrolling patients in the DOSE-VF study. In addition, the pandemic has contributed to an enormous turnover of paramedics in many of the participating services. Dr. Cheskes has prepared excellent training videos for all new hires, but without the ability to engage in face to face training, there are now a number of paramedics in each service who have had no "hands on" training in either of the intervention techniques. While video training is adequate, it cannot replace in-person training of all new service hires.

Overall, despite the incredible effort and dedication by all involved, the **DSMB recommends the DOSE VF RCT be stopped at this time in all sites except for Ottawa Paramedic Service due to the impact of the pandemic on the study protocol.** The DSMB unanimously agreed there was no need for an interim analysis and the decision to terminate the trial early should be based on the compliance concerns and not the outcomes. For the reasons listed above, it does not seem feasible to continue to enrol patients in this study with the same high standard this study was praised for in the pre-COVID period. The reduced compliance and paramedic service issues related to the COVID-19 pandemic are likely to disproportionately impact the intervention arms, biasing the results towards the null. While there is a concern of the trial being under powered by stopping early, it seems unlikely that continued enrolment with reduced compliance would help to rectify this concern. The DSMB also discussed the option of pausing the trial again and restarting once COVID-19 settles down and paramedic staffing issues have resolved, but this does not seem feasible.

The exception to stopping the trial would be the Ottawa Paramedic Service. The DSMB believe all attempts should be made to allow this service to continue in the current study arm until they have completed this arm (May 2022) to meet the minimum cross over requirements consistent with the trial protocol.

Lastly, the DSMB suggested the PI and the Steering Committee consider altering the patient population analyzed for the primary outcome from the *a priori* intention-to-treat population to a per-protocol population, which is most likely to benefit from the intervention. This may eliminate some of the noise that may have entered into the trial during COVID.

Respectfully submitted,

Benjamin Abella, MD MPhil FACEP
Professor and Vice Chair for Research
Department of Emergency Medicine
Director, Center for Resuscitation Science

Jim Christenson MD FRCPC
Professor, University of British Columbia,
Department of Emergency Medicine
Executive Medical Director, BC Emergency Medicine Network
Co-Director, BC Resuscitation Research Collaborative

Gerald Lebovic, PhD
Investigator, AHRC, Unity Health Toronto
Assistant Professor, IHPME, University of Toronto