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

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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 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 vector change defibrillation) 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 vector change defibrillation (anterior-posterior compared to anterior-anterior 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 vector change (change of defibrillation pads from anterior-anterior to an anterior-posterior pad position) defibrillation. The primary outcome will be survival to hospital discharge. Secondary outcomes will include 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 vector change 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
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. 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). 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. 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. 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 To date, over 2,300 paramedics in Ontario have been trained in the technique of DSED and vector change defibrillation, and 4 large sites (Toronto, Peel, Halton and Simcoe) have been 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=113 as of April 4, 2019) in the participating Emergency Medical Services have had paramedics successfully apply both vector change and DSED. The DOSE-VF Pilot RCT demonstrated that the protocol is feasible and well accepted by paramedics in the field. We have as well been able to determine the number of cases occurring in each Region during the pilot RCT allowing us to accurately calculate the number of patients required to perform an adequately powered definitive RCT. 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 vector change defibrillation) 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 vector change defibrillation (anterior-posterior compared to anterior-anterior 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 defibrillation attempts each separated by 2 minutes of CPR.

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

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

Outcomes: The primary outcome will be survival to hospital discharge. Secondary outcomes will include 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).

**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, presumed pregnancy, 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 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.\textsuperscript{19, 20} Two treatment strategies (DSED and vector change) 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.\textsuperscript{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 vector change) for six months. Each service will apply one 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 be registered with clinicaltrials.gov.

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. Patients suffering in-hospital cardiac arrest 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-anterior 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 EMS agencies randomized to standard defibrillation, all subsequent defibrillation attempts will occur through pads placed in an anterior-anterior configuration as noted in Appendix 1.

Strategy 2 (Vector Change Defibrillation): For EMS agencies randomized to vector change 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-anterior configuration will occur during the two-minute cycle of CPR following the third shock with minimal interruptions in CPR.

Strategy 3 (DSED): For EMS agencies randomized to DSED, paramedics will apply a second set of defibrillation pads after the first three shocks (via a second EMS 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 (EMS agency) will be randomized to standard defibrillation, defibrillation using vector change, or DSED (see attached timeline in Appendix 2). All clusters will crossover between standard defibrillation, defibrillation using vector change 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. 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 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 recognize that neurologically intact survival to hospital discharge would be the most relevant patient-centered outcome for this trial; however, capture of this data would require intensive follow-up assessments and presents a level of complexity and cost that would go beyond the possible funding for our research. Furthermore, our previous work has demonstrated that most patients who survive to hospital discharge after out-of-hospital cardiac arrest do so with good
neurological outcomes, suggesting our primary outcome of survival to hospital discharge is reasonable.\textsuperscript{23}

\textbf{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

We hypothesize that DSED and vector change 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 vector change or DSED strategies are employed as per our protocol, compared to standard care.

Using these baseline estimates, and assuming a fixed number of EMS clusters (n=6), we will enroll approximately 20-40 patients per cluster over one year. Data from the internal pilot RCT will be included in the final analysis. The study design assumes that each cluster will cross over twice to receive each of three treatment approaches (standard defibrillation, DSED and vector change defibrillation) 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. 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; 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 vector change) 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 vector change defibrillation to standard defibrillation. A secondary analysis will compare DSED to vector change defibrillation. We hypothesize that resuscitation involving DSED and resuscitation involving vector change 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.\textsuperscript{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 (modified intention-to-treat analysis as described in Appendix 4); a secondary analysis will involve a per-protocol analysis to account for situations where two defibrillators are not readily available in the DSED arm. 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). The binary primary outcome, survival to hospital discharge, will be compared across the arms of DSED and vector change defibrillation as an adjusted odds ratio with 95\% confidence intervals (CIs) using the standard arm as the reference group.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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, termination of VF at first chest compression pause defined as the absence of VF after each interventional or standard shock, 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). 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.)

**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 a blinded interim data safety analysis to assess for lower than anticipated rates of survival between the three treatment groups. The committee will meet at six month 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 a blinded interim data analysis and will advise if sample size modification if necessary. Sample size modification based on blinded interim results is relatively well understood and is unlikely to introduce bias or raise major concerns.\textsuperscript{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.

\textit{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 vector change 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 and Good Clinical Practice Guidelines.

*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.
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