A PRAGMATIC RANDOMIZED CLINICAL TRIAL COMPARING RECTILINEAR BIPHASIC WAVEFORM AND BIPHASIC TRUNCATED EXPONENTIAL WAVEFORM SHOCKS FOR CARDIOVERSION OF ATRIAL FIBRILLATION (ZOLL VS LIFEPAK-RCT)

NCT05992623

Document Date 5/22/2023

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Inova Protocol #:	**U23-04-5042**
External IRB Protocol #:	NA
Funding Source:	N/A
Drug or Device Name(s):	Zoll Series R Defibrillator Physiocontrol Lifepak Series 15/20 Defibrillator
FDA IND/IDE #:	N/A
Protocol Date:	3/2/23
Sponsor-Investigator:	Inova Heart and Vascular Institute
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Supplied Agent(s): Commercial

Study Exempt from IND Requirements per 21 CFR 312.2(b) as determined by FDA.

Protocol Type / Version # / Version Date:

Original / Version # 1 / Version Date 03/02/2023

SUMMARY OF CHANGES

Inova Study #: U23-04-5042

External IRB Protocol #: n/a

Protocol Date: 03/02/2023

Protocol Modification #: 1

REVISION HISTORY

#	Section	Page(s)	Summary of Changes	Consent Change (Y/N)
1.				
2.				
3.				
4.				
5.				

ABSTRACT

Atrial fibrillation (AF) is a major cause of cardiovascular morbidity and mortality, affecting more than 46 million people worldwide.[1] Direct current cardioversion (DCCV) is used to terminate an episode of symptomatic or hemodynamically unstable AF. The success rate for DCCV is 90-95% and is dependent on patient and procedural characteristics including obesity, use of antiarrhythmic drugs, pad placement, type of shock waveform and shock energy. Biphasic defibrillation waveform shocks improve DCCV success rates for AF to normal sinus rhythm (NSR) compared to monophasic shocks. Various biphasic shock waveforms are available: The Rectilinear Biphasic Waveform (RBW) is used by the Zoll series R defibrillator while the Biphasic Truncated Waveform (BTW) is used in the FDA approved Lifepak model 15 and 20 defibrillators. Despite their routine use in clinical practice, no adequately powered prospective head-to-head randomized controlled trials (RCT) have compared the safety or efficacy of the two biphasic waveforms for DCCV of AF to NSR.

The primary objectives for this pragmatic prospective randomized controlled trial are to 1) compare the efficacy of first shock DCCV from AF to NSR using anterolateral pad placement and a full-output 200J RBW synchronized shock from a Zoll series R defibrillator or a full output 360J BTW synchronized shock from a Lifepak 15 or 20 defibrillator; 2) compare the DCCV efficacy of first or second full output shock 3) compare the DCCV efficacy of third or fourth full output shock after treatment group cross over after first failing 2 consecutive full output shocks from the originally assigned treatment group. The secondary objective is to compare the frequency of skin irritation or damage after first or second shock cardioversion from either defibrillator.

Data will be derived from approximately 560 patients arriving to Inova sites of care in AF scheduled to undergo either AF ablation with expected DCCV or elective stand-alone AF DCCV. Patients will be included if they are in AF prior to their procedure and are willing to sign the consent form and comply with the research procedures. Participants will be excluded if they are in a rhythm other than AF on arrival to IHVI, have not been appropriately anticoagulated with warfarin or direct oral anticoagulant, or have known left atrial appendage thrombus prior to their procedure.

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition of Terms
DCCV	Direct Current Cardioverison
RBW	Rectilinear Biphasic Waveform
BTW	Biphasic Truncated Waveform
J	Joules
AF	Atrial Fibrillation
IHVI	Inova Heart and Vascular Institute
NSR	Normal Sinus Rhythm

PROTOCOL SYNOPSIS

Study Title:	A Pragmatic Randomized Clinical Trial Comparing Rectilinear Biphasic Waveform and Biphasic Truncated Exponential Waveform Shocks for Cardioversion of Atrial Fibrillation (Zoll vs Lifepak-RCT)
Source of Funding:	N/A
Clinical Phase:	N/A
Study Rationale:	Atrial fibrillation (AF) is a major cause of cardiovascular morbidity and mortality, affecting more than 46 million people worldwide.[1] Direct current cardioversion (DCCV) is used to terminate an episode of symptomatic or hemodynamically unstable AF. The success rate for DCCV is 90-95% and is dependent on patient and procedural characteristics including obesity, use of antiarrhythmic drugs, pad placement, type of shock waveform and shock energy. Biphasic defibrillation waveform shocks improve DCCV success rates for AF to normal sinus rhythm (NSR) compared to monophasic shocks. Various biphasic shock waveforms are available: The Rectilinear Biphasic Waveform (RBW) is used by the Zoll series R defibrillator while the Biphasic Truncated Exponential Waveform (BTE) is used in the FDA approved Lifepak 15 or 20 defibrillator. Despite their routine use in clinical practice, no adequately powered prospective head-to-head randomized controlled trials (RCT) have compared the safety or efficacy of the two biphasic waveforms for DCCV of AF to NSR. The primary objectives for this pragmatic prospective randomized controlled trial are to 1) compare the efficacy of first shock DCCV from AF to NSR using an anterolateral pad placement and full-output 200J RBW synchronized shock from a Zoll series R defibrillator and a full output 360J BTW synchronized shock from a Lifepak 15 or 20 defibrillator; 2) compare the DCCV efficacy of first or second full output shock 3) compare the DCCV efficacy of first or second crossover full output shock after first failing 2 consecutive full output shocks from the other

	defibrillator. The secondary objective is to compare the frequency of skin irritation or damage after first or second shock cardioversion from either defibrillator.
Study Objective(s):	Primary: 1. To compare the efficacy of a single 200J RBW shock and a single 360J BTE shock 2. To compare the efficacy of one or two consecutive 200J RBW or 360J BTE shocks 3. To measure the efficacy of cross over from RBW to BTE or BTE to RBW after failing 2 consecutive full output shocks with the first waveform Secondary: 1. To compare the frequency of adverse events after one or two 200J RBW or 360J BTE shocks
Test Product(s)/Agent(s):	1. Zoll Series R Defibrillator (RBW shock waveform, maximum output 200J) 2. Physiocontrol Lifepak 15 or 20 Defibrillator (BTE shock waveform, maximum output 360J)
Study Design:	Single center, investigator-initiated, open label prospective randomized controlled trial
Participant Population Key Criteria for Inclusion and Exclusion:	Inclusion Criteria: ▪ Adults aged ≥18 years of age in AF scheduled to undergo DCCV or catheter ablation with expected DCCV Exclusion Criteria: ▪ Patients with arrhythmias other than AF, hemodynamically unstable AF, untreated hyperthyroidism, known or suspected pregnancy, those in another trial. Patients will be required to have received sufficient anticoagulation or computed tomography angiography scan or transesophageal echocardiogram documenting the absence of intracardiac thrombi.
Number of Participants:	A total of 560 unique study subjects will be enrolled.

Study Duration:	Each subject's participation will last from screening until 1 minute after the final DCCV shock is delivered.
Study Phases:	1. Screening: Patients arriving in AF scheduled to undergo DCCV or AF ablation with possible DCCV at an Inova site of care will be screened in the peri-procedure holding area. 2. Intervention: Patients will be randomized to a Zoll or Lifepak defibrillator to perform the DCCV. All shocks will be full output (200J for Zoll shocks and 360J for Lifepak shocks). Follow up will be assessment and documentation of rhythm 1 minute after the last shock is delivered.
Efficacy Evaluations:	1. Proportion of patients in NSR by ECG or monitor 1 minute after the first DCCV shock. 2. Proportion of patients in NSR by ECG or monitor 1 minute after the first or second DCCV shock. 3. Proportion of patients in NSR by ECG or monitor 1 minute after a third or fourth crossover treatment assignment shock after failing first and second shock on original treatment assignment.
Safety Evaluations:	1. Number of patients with skin redness, pain or discomfort under the shock electrodes (excluding those with cross-over) 2. Number of patients with arrhythmic events (asystole, atrioventricular block, transient bradycardia or ventricular arrhythmia) within 10 minutes of the last DCCV shock 3. Frequency of pacemaker or ICD dysfunction after shock among patients with prior pacemaker or defibrillator implant
Statistical and Analytical Plan:	Based on the best available literature we expect the first shock DCCV success rate to be 93% in our population. A total sample size of 538 subjects (269 in each group) will be needed to provide 80% power to reject the null hypothesis (a difference of efficacy < 5%). The analysis will be performed on the intention-to-treat population. The proportions will be compared using both risk difference and risk ratio with corresponding 95% CI. Effects of treatment will be estimated by modified

	Poisson regression using generalized estimating equations. Outcomes will be compared across pre-specified subgroups and testing will be performed for interactions (sex, body mass index, first or > 1 AF episode, AF type, DCCV location).
Data and Safety Monitoring Plan:	The study PI will be responsible for study safety. One interval analysis will be performed after 50% trial enrollment. No DSMB will be assembled.

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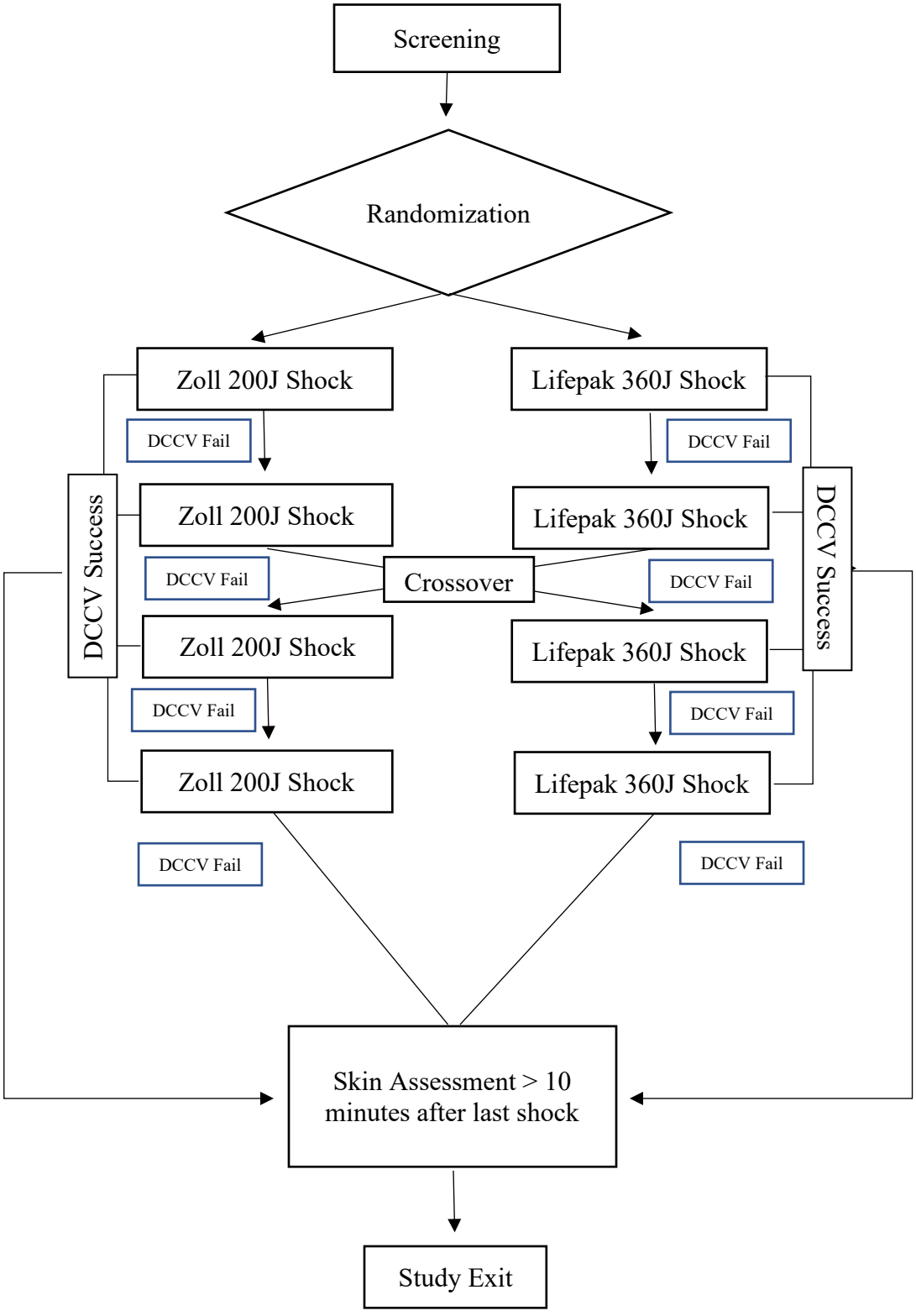
Screening
Randomization
Zoll 200J Shock
Lifepak 360J Shock
DCCV Fail
DCCV Fail
DCCV Success
Zoll 200J Shock
Lifepak 360J Shock
DCCV Success
DCCV Fail
Crossover
DCCV Fail
Zoll 200J Shock
Lifepak 360J Shock
DCCV Fail
DCCV Fail
Zoll 200J Shock
Lifepak 360J Shock
DCCV Fail
DCCV Fail
Skin Assessment > 10 minutes after last shock
Study Exit

Study Phase	**Screening (Pre-Op)**	**Treatment/Intervention (EP Lab or CDU Procedure Suite)**
Informed Consent/Assent	X	
Review Inclusion/Exclusion Criteria	X	
Duration of AF Assessment (< 7 days, 7 days-365 days, > 365 days	X	
Months since AF diagnosis	X	
Prior DCCV?	X	
CHA2DS2VASC score	X	
Moderate or Severe Valvular Disease?	X	
Heart Failure with Reduced Ejection Fraction?	X	
Body Mass Index	X	
Date of Birth	X	
Sex	X	
Pregnancy Test	X	
Amiodarone (yes/no)	X	
Flecainide (yes/no)	X	
Beta blockers (yes/no)	X	
Ace Inhibitor or ARB (yes/no)	X	
Randomization	X	
DCCV		X
ECG or Monitor 1 minute after 1st shock		X
Adverse Event Assessment 10 minutes after shock or at conclusion of procedure		X

1. BACKGROUND

Direct current cardioversion (DCCV) is widely used for restoring normal sinus rhythm (NSR) in patients with atrial fibrillation (AF)[1,2]. More than 1500 DCCV procedures were performed in the Inova health system in 2022. Identifying the safest and most efficacious method is important. Despite decades of clinical use, the ideal shock waveform and energy for DCCV from AF to NSR are still unknown. Two FDA approved external defibrillation devices (Zoll series R and Lifepak 15/20) are used to deliver DCCV shocks in clinical practice in the Inova Health System. These devices differ in shock waveform and maximum energy delivery. The Zoll Series R device uses a Rectilinear Biphasic Waveform (RBW) with a maximum energy of 200 Joules while the Physiocontrol Lifepak Series 15/20 devices use a Biphasic Truncated Exponential (BTE) Waveform with a maximum energy of 360 Joules. Four small studies (n=50-101 patients per group) have compared the efficacy of RBW and BTE waveforms for DCCV of AF to NSR[3,4,5,6]. None of the studies were adequately powered to detect clinically meaningful differences in efficacy or safety of the waveforms. All 4 studies used a protocol starting with low energy shocks (50-100J) and escalating the output over multiple shocks. Since these studies have been published, maximum energy shocks were found to be more effective and safer than escalating low-energy shocks for DCCV[7] and maximum energy first shocks are now recommended in European guidelines[8]. We therefore propose an adequately powered randomized controlled trial (RCT) evaluating the efficacy and safety of maximum energy RBW and BTE shock waveforms delivered by the Zoll series R and Physiocontrol Lifepak Series 15/20 devices respectively.

1.1 Study Disease(s) or Condition(s)

AF is the most common cardiac arrhythmia affecting more than 46 million people worldwide. More than 86,000 patients have been diagnosed with AF in the Inova health system in the past year. AF is frequently associated with symptoms of fatigue, shortness of breath and palpitations. DCCV is a commonly performed procedure to temporarily restore NSR in patients with symptomatic AF or in those with hemodynamically intolerable AF.

1.2 Product(s) / Agent(s)

The Zoll series R defibrillator is an FDA approved device with indications for defibrillation of cardiac arrest where there is an apparent lack of circulation and for synchronized DCCV of certain atrial and ventricular arrhythmias. It is indicated for adult and pediatric patients. The device is connected to the patient through the one-step cable and the manufacturer recommends also connecting a separate ECG cable. The Zoll series R defibrillator has been deployed across the Inova health system and is currently available for clinical use in all clinical areas performing DCCV. For this study the device will be used on label and according to manufacturer recommendations. All shocks will be synchronized and delivered in the manual mode at 200J through the one touch hands-free pads. No shocks will be delivered through paddles. The Physiocontrol Lifepak 15 and 20 monitor/defibrillators are FDA approved devices with indications for termination of certain fatal arrhythmias such as ventricular fibrillation and symptomatic ventricular tachycardia. Delivery of energy in synchronized mode is a method for

treating AF, atrial flutter, paroxysmal supraventricular tachycardia, and in relatively stable patients with ventricular tachycardia. The Lifepak 15 and 20 defibrillators have been deployed across the Inova health system and are currently available for clinical use in all clinical areas performing DCCV. For this study all shocks will be delivered in the manual mode at 360J synchronized through hands-free pads. No shocks will be delivered through paddles.

1.3 Rationale

Four small studies (n=50-101 patients per group) have compared the efficacy of RBW and BTE waveforms for DCCV of AF to NSR[3,4,5,6]. None of the studies were adequately powered to detect clinically meaningful differences in efficacy or safety of the waveforms and all used escalating low-energy shocks. Since these studies have been published, maximum fixed energy shocks were found to be more effective than escalating low-energy shocks for DCCV and maximum energy first shocks are now suggested in European guidelines[8]. We therefore propose an adequately powered randomized controlled trial (RCT) evaluating the efficacy and safety of maximum energy RBW and BTE shock waveforms delivered by the Zoll series R and Lifepak 15 and 20 devices respectively.

1.4 Relevant Literature and Data

In 1959 Lown developed a direct current waveform to improve efficacy and reduce adverse events associated with defibrillation performed with alternating current. The monophasic waveform he developed was in use until the 1980s when biphasic waveforms were shown to further improve defibrillation success. Several biphasic waveforms have been developed including the BTE and RBW waveforms. These waveforms have been incorporated into competing FDA approved devices manufactured by Zoll, Phillips, and Physiocontrol/Medtronic.

- The first comparative study of biphasic DCCV shock waveforms was published in 2003[3]. Investigators randomized 101 patients with AF to DCCV using escalating RBW shocks from a Zoll M series defibrillator (50, 100, 200, 200J) or escalating BTE shocks from a Physiocontrol Lifepak-12 defibrillator (50, 100, 200, 200J). If the fourth shock at 200J failed in either arm a single 360J shock was delivered from the BTE device. Patches were placed in an antero-posterior location. The overall efficacy was 97.9% in the BTE group and 100% in the RBW group (p=0.29). The study was underpowered to detect a clinically significant difference between groups. Enrollment would have allowed the study to detect an efficacy difference of 20% or more.
- The second observational study was published in 2004[4]. Patients with AF underwent DCCV with a series of escalating RBW shocks from a Zoll series M

defibrillator (50,100,150, 200J) or a BTE shock (50,100,150, 300, 360J) from a Medtronic Physiocontrol Lifepak 12 defibrillator. If DCCV was unsuccessful at the maximum deliverable energy patients were crossed over to the other device. Patches were placed in an antero-posterior location. 145 patients were enrolled but treatment allocation was not randomized because of patient refusal or physician refusal to participate in the study. The success rate was 97% in both groups (p=1.0). 2/71 patients in the RBW group failed maximum energy shock (200J) and crossed over to the 360J RBW shock and were successfully converted. 2/71 patients in the BTE group failed maximum energy shock (360J) and crossed over to the RBW group. Both also failed the RBW shock.

- The third comparative study of the RBW and BTE waveforms was published in 2005[5].The investigators randomized 188 subjects with AF in a 1:1 fashion to receive escalating low energy RBW shocks (50, 75, 100, 120, 150, 200 J) or BTE shocks (50, 70, 100, 125, 150, 200, 300, 360 J). The shock strength was escalated until success or maximum energy was delivered. If maximum energy shock failed, the patient crossed over to the opposite waveform. 47 patients were excluded leaving a total of 141 patients (71 in RBW and 70 with BTE shocks). The authors found a maximum energy success rate of 93% in patients receiving a RBW shock and 97% in patients receiving a BTE shock (p=0.44). Unfortunately, the small study sample size would have allowed the authors to detect a minimum difference in success rate of 14% or more, while a clinically relevant efficacy difference of 5% or more was impossible to detect.
- The fourth comparative study of commercially available biphasic waveforms was published in 2013[6]. The investigators randomized 199 patients to receive DCCV using either a RBW from a Zoll series R defibrillator or BTE from a Phillips Heartstart XL defibrillator using 50, 100, 150, 200, 200 J. The shock strength was escalated until success or maximum energy was delivered. 95% of patients in the RBW and 90.9% of patients in the BTE arms successfully converted to NSR (P=0.838). Unfortunately, the small study sample size allowed the study to detect differences in efficacy of 20% or more and they did not deliver maximal energy (360J) shocks using the BTE waveform, limiting the clinical applicability of the findings.
- Since the 4 comparative studies were published, a randomized controlled study in 2021 showed anterolateral patch placement improved DCCV success rate compared to anteroposterior placement[9]. Further, a DCCV protocol using fixed maximum energy shocks was found to be more effective than escalating low-energy shocks[7]. No adequately powered studies have compared a first maximum shock efficacy of RBW (200J) to BTE (360J) waveforms incorporating these recommendations and an anterolateral patch location.

Correlative Studies Background

1.4.1 NA

1.5 Compliance Statement

This study will be conducted in full accordance with all applicable Inova Health System's Federalwide Assurance (FWA), Research Policies and Procedures, and all applicable Federal and State laws. These regulations include, but are not limited to 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 812, and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH).

The investigators will perform the study in accordance with this protocol, will obtain consent and/or assent (unless waived by the IRB of record), and will report unanticipated problems involving risk to participants or others and potential serious or continuing non-compliance in accordance with the Inova Health System's Office of Research Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research participants during and after the study.

2. OBJECTIVES

2.1 Primary Objectives

2.1.1 To compare the efficacy of a single 200J RBW shock and a single 360J BTE shock

2.1.2 To compare the efficacy of one or two consecutive 200J RBW or 360J BTE shocks

2.1.3 To measure the efficacy of cross over from RBW to BTE or BTE to RBW after failing 2 consecutive full output shocks with the first waveform

2.2 Secondary Objectives

2.2.1 To compare the frequency of adverse events after one or two 200J RBW or 360J BTE shocks. Patients undergoing cross-over will be excluded from this analysis.

3. SETTINGS

3.1 Study Sites

The study will be conducted at one investigative site in the United States.

The following investigative sites will be conducting this study:

Inova Heart and Vascular Institute 3300 Gallows Rd. Falls Church, VA 22042	Inova Alexandria Hospital Heart and Vascular Center 4320 Seminary Road, Alexandria VA 22304	Inova Loudoun Hospital Heart and Vascular Center 44045 Riverside Pkwy, Leesburg, VA 20176

3.2 Community Involvement

Not applicable

3.3 Outside of Organization

Not applicable

4. RESOURCES AVAILABLE

4.1 Conducting Research

30-35 unique patients undergo DCCV for AF in the cardiac diagnostic unit or electrophysiology labs at IHVI each week (1560/year). Assuming 50% of these subjects meet eligibility criteria, we expect to be able to complete enrollment of the 560 patients in approximately 6 months.

The PI will dedicate 5% of his time to conducting and completing the research. Both the Zoll series R and Lifepak 15/20 defibrillators, connector cables, and pads are available in the EP labs and the CDU at IHVI, IAH, and ILH hospitals.

4.2 Medical and/or Psychological Resources

Not Applicable

5. INVESTIGATIONAL PLAN

5.1 General Schema of Study Design

5.1.1 Hypothesis

We hypothesize that the maximal output first shock efficacy of RBW and BTE shocks differs by more than 5%.

5.1.2 Phase of the Trial

This is a single center, investigator-initiated, open-label, pragmatic randomized controlled assessment trial.

5.1.3 Study Treatment

Patients with AF will be randomized to receive either a full output synchronized 200J shock using a RBW waveform from a Zoll R series defibrillator or a full output synchronized 360J shock using a BTE waveform from a Lifepak Series 15/20 defibrillator.

Success will be defined as NSR 1 minute after the shock. Patients who do not have first shock success will have a second full output shock ≥1 minute after the first shock. Patients who do not have success after a second full output shock will be crossed over to the other defibrillator waveform and receive up to 2 full output shocks with a minimum of 1 minute between each shock to ascertain the outcome of the immediately prior shock.

5.2 Product(s) / Agent(s)

5.2.1 Handling, Storage, Accountability, and Preparation

Both the Zoll Series R defibrillator and the Lifepak 15 and 20 defibrillators and the necessary cables and pads are stored in the cardioversion procedure rooms and the Electrophysiology labs in IHVI, IAH, and ILH hospitals.

5.2.1.1 Acquisition and Accountability

Both defibrillators are already available for clinical use in both the cardioversion procedure rooms and Electrophysiology labs in IHVI, IAH, and ILH hospitals.

5.2.1.2 Storage and Stability

Not applicable

5.2.1.3 Preparation

Not applicable

5.3 Allocation to Treatment Groups and Blinding/Randomization

Patients will be randomly allocated to either treatment group in a 1:1 fashion. Randomization will be blocked by treatment location (Electrophysiology labs versus other environments due to the differing pad locations in these two environments). A randomization sequence will be created in the RedCAP file. Randomization envelopes will be created and stored in the pre-procedure electrophysiology holding areas or electrophysiology labs or the DCCV procedure areas. In the envelope will be the case report form with the treatment assignment listed on it. Prior to the DCCV procedure staff will open an envelope to learn the treatment assignment and then use the assigned defibrillator. Patients, staff, and investigators will be unblinded. The clinical staff will complete the CRF. They will attach the rhythm strip or ECG acquired 1 minute after the shock and place it back in the envelope. They will seal the envelope and place it in a secure location to be gathered by the study team.

6. STUDY TIMELINE

6.1 Individual Participation

The study duration per participant will be up to 1 day. Screening, treatment and the 10 minute follow up will all occur at the time of the planned DCCV procedure.

6.2 Study Timeline

6.2.1 Treatment: 1 day

6.2.2 Follow-up: same day

6.2.3 Estimated Closure: 9-12 months after initiation.

7. PARTICIPANT SELECTION

Participants that do not meet all the inclusion criteria may not be enrolled, unless a prior exception request is approved by the sponsor and submitted for IRB review and approval. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

7.1.1 Index/Case Participant Eligibility Criteria

7.1.1.1 Age ≥ 18 years

7.1.1.2 In AF on presentation with plan for DCCV in either the Electrophysiology lab or DCCV procedure area.

7.2 Exclusion Criteria

7.2.1 Index/Case Participant Exclusion Criteria

7.2.1.1 Participants who are receiving any other investigational agents.

7.2.1.2 Parents/guardians or participants who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

7.2.1.3 Patients with arrhythmias other than AF

7.2.1.4 Patients with hemodynamically unstable AF

7.2.1.5 Patients with untreated hyperthyroidism

7.2.1.6 Patients with known or suspected pregnancy

7.2.1.7 Patients without sufficient anticoagulation or a transesophageal echocardiogram or computed tomography scan documenting the absence of intracardiac thrombi

7.3 Lifestyle Considerations

7.3.1 Not Applicable

7.4 Vulnerable Populations

Vulnerable populations will not be enrolled in this study. Both men and women of all races and ethnic groups are eligible for this trial.

8. RECRUITMENT METHODS

8.1 Methods

8.1.1 Recruitment

Patients in AF presenting to the pre-procedure holding areas prior to DCCV or catheter ablation of AF at Inova care sites will be screened for possible enrollment. Patients will be provided an opt-out information sheet before being enrolled in the study.

8.1.2 Screening

Screening will occur immediately before the patient undergoes a DCCV procedure. Screening will be performed by the performing physician investigator. Because the inclusion criteria and exclusion criteria are identical to those for DCCV of AF, no additional chart review will be needed by the physician investigator for study screening. Prior to a DCCV procedure the chart is reviewed and a face to face discussion is had with the patient. These processes will be used to also screen for study inclusion since the same data will be used to determine if they are a candidate for DCCV AND whether they can be included in the study. Screening will occur on site just prior to scheduled DCCV procedures by the investigators performing the procedure. Screening will occur without prior consent/assent/HIPPA authorization under a HIPPA and/or Informed Consent Waiver.

Projected Participants

Recruitment will stop when approximately 560 participants are screened/consented. It is expected that approximately 560 participants will be enrolled to produce 544 evaluable participants.

8.2 Materials

Not applicable

8.3 Underrepresented Populations

Patients of all races, ethnicities, and sexes will be enrolled.

9. STUDY PROCEDURES

9.1 Screening Visit

9.1.1 Informed Consent/Assent/HIPAA Authorization

We will seek an alteration of consent, a waiver of documentation of consent, and an alteration of HIPPA for this study.

9.1.2 Physical Exam

Not Applicable

9.1.3 Vital Signs

Heart rate and blood pressure before and after DCCV will be obtained. Patients

with hypotension and tachycardia will be deemed to have hemodynamically unstable AF and will be excluded.

9.1.4 Laboratory Tests

Not applicable

9.1.5 Medical Record Review

This will be performed as part of the screening procedure prior to providing the information sheet.

9.2 Study Intervention Visit

9.2.1 At the study visit the patient will be connected to the randomly allocated defibrillator, connector cable, and pads. Pads will be placed in an anterolateral location unless this is impossible, in which case pads will be applied in alternative locations. After sedation is provided the patient will undergo DCCV at full output (200J for the Zoll Series R device and 360J for the Lifepak Series 15/20 device). After the procedure is complete the pads will be removed and the site assessed for erythema or burns 10 minutes or more after the last administered shock.

9.3 Follow-Up

Not applicable

9.4 Unscheduled Visits

Not applicable

9.5 Lost to Follow-Up

Not applicable

10. STUDY ADMINISTRATION

10.1 Study Intervention(s) Administration

10.1.1 Study Intervention Description

The study will compare safety and efficacy of full output shocks from two commercially available FDA approved defibrillators.

The Zoll R series defibrillator was approved with the following indications on 12/27/2017 (downloaded from www.accessdata.fda.gov on 3/3/2023.)

The R Series System Is Indicated For Defibrillation On Victims Of Cardiac Arrest Where There Is Apparent Lack Of Circulation As Indicated By:1) Unconsciousness;2) Absence Of Breathing; And 3) Absence Of Pulse. The R Series System In The Manual Mode Is Indicated For Synchronized

Cardioversion Of Certain Atrial Or Ventricular Arrhythmias. A Qualified Physician Must Decide When Synchronized Cardioversion Is Appropriate. The R Series System Semiautomatic And Manual Mode Is Indicated For Use In Early Defibrillation Programs Where The Delivery Of A Defibrillator Shock During Resuscitation Involving CPR, Transportation, And Definitive Care Are Incorporated Into A Medically-Approved Patient Care Protocol. The R Series System Semiautomatic And Manual Mode Is Indicated For Adult And Pediatric Patients.

The Lifepak model 15 and 20 Monitor/Defibrillator was approved with the following indications on 8/22/2018 (downloaded from www.accessdata.fda.gov on 3/3/2023.) Manual defibrillation is indicated for the termination of certain potentially fatal arrhythmias, such as ventricular fibrillation and symptomatic ventricular tachycardia. Delivery of this energy in the synchronized mode is a method for treating atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia and, in relatively stable patients, ventricular tachycardia.

10.1.2 Dosing and Administration

The dose of energy for all shocks delivered from the Zoll series R defibrillator will be 200J. The dose of energy for all shocks administered from the Lifepak series 15/20 will be 360J. A patient may receive a second shock at the same output if the first shock is unsuccessful. If the second shock is unsuccessful the original defibrillator and pads will be removed, and the alternate defibrillator applied.

10.2 Measures to Minimize Bias: Randomization

10.2.1 Randomization

Patients will be randomly allocated in a 1:1 fashion to RBW or BTE waveforms and their associated maximal outputs. Randomization codes will not be broken.

10.2.2 Blinding

Neither the investigators nor patients will be blinded to their treatment allocation.

10.2.3 Unblinding

Not applicable

11. DATA AND SPECIMEN COLLECTION AND MANAGEMENT

11.1 Data Collection and Management

Data will be collected by study staff on case report forms. The CRF will be completed by the physician investigator at the conclusion of the procedure. The CRFs will be placed in a sealed envelope and stored in a locked file cabinet in the EP lab or CDU care area. The

study staff will collect the completed forms weekly.The study staff will not need to be present during enrollment or CRF completion. These forms will be scanned and the associated file stored in REDCAP as source documents. Pre and post DCCV monitoring strips or ECGs to document pre DCCV AF and post DCCV rhythm will be stored in PDF format or printed on paper and scanned as source documents into the CRF.

11.1.1 Storage and Future Use-

All data will be stored in a REDCAP database. Source documents including paper CRF forms will be scanned and files attached to the REDCAP database then shredded.

11.1.2 Retention/Access

Data will be stored in REDCAP according to Inova ORI policy. No specimens will be collected. The study PI and study coordinators will have access to the REDCAP database. Paper case report forms will be stored in a secure location in the procedure area and will be picked up weekly by the study coordinator for entry into the REDCAP database. Records will be retained in the REDCAP registry according to Inova's record retention policy, currently a minimum of 3 years after study completion.

11.1.3 Data Fields

Please see the case report form for exact data collected. Identifiers collected will include name, Inova medical record number, date of birth, and date of DCCV procedure.

11.2 Specimen Collection and Management

Not Applicable

11.3 Security

All data will be stored in a REDCAP database and access will be provided only to the PI and CRC. All paper source documents will be scanned and then the originals will be shredded.

11.3.1 Anonymization, De-Identification and/or Destruction

Data will remain in the REDCAP registry and all analyses will be performed either within the REDCAP registry or on an Inova provisioned computer behind the Inova firewall. No data will be stored outside of REDCAP.

11.4 Release of Locally Banked Data

Not applicable

11.5 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Inova Health System institutional policies and HIPAA on participant privacy. The Investigator and other site personnel will not use such

data and records for any purpose other than conducting the study.

No identifiable data will be used for future use without first obtaining IRB approval or determination of exemption.

11.5.1 Certificate of Confidentiality

Not applicable

12. DATA ANALYTICS

12.1 Study Endpoints

Efficacy assessments for the primary endpoints will occur using data obtained at screening and the DCCV study visit. Specifically, the endpoint of NSR will be acquired by monitoring strip or 12 lead ECG 1 minute after each DCCV shock is delivered.

Primary Endpoints

12.1.1 The frequency of NSR one minute after a single full output DCCV shock is delivered by a Zoll Series R RBW waveform defibrillator and a Lifepak Series 15/20 BTE waveform defibrillator.

12.1.2 The frequency of NSR one minute after the first or second full output DCCV shock is delivered by a Zoll Series R RBW waveform defibrillator and a Lifepak Series15/20 BTE waveform defibrillator.

12.1.3 The frequency of NSR one minute after the first or second full output DCCV shock is delivered by a Zoll Series R RBW waveform defibrillator and a Lifepak Series 15/20 BTE waveform defibrillator after crossing over from the alternative defibrillator after failing 2 consecutive full output shocks at maximum output.

Secondary Endpoints

12.1.4 The frequency of adverse events including skin irritation, pain, or burning; arrhythmic events including asystole, atrioventricular block, transient bradycardia or ventricular arrhythmia within 10 minutes of the last DCCV shock; and the frequency of pacemaker or ICD dysfunction after shock among patients with prior pacemaker or defibrillator implant. Transient bradycardia will be defined as symptomatic bradycardia requiring the use of temporary pacing, atropine, isuprel, or epinephrine for rate support. The secondary safety endpoint will be assessed only among patients who do not cross-over from one defibrillator to the other.

12.1.5 End of Study Definition

A participant is considered to have completed the study If he or she has completed all phases of the study including screening, enrollment,

procedure and the 10 minute skin assessment after pad removal.

The end of the study is defined as completion of the last visit shown in the Schedule of Activities.

12.2 Analytics

All analyses will be performed on an intention to treat basis. We calculated the sample size on the basis of the 3 prior randomized studies that compared RBW and BTE shocks for DCCV of AF. In these studies, the mean overall shock success was 90-97% and the first shock success varied from 54%-90% albeit the first shock was delivered at a lower energy than maximum output. We therefore estimate that the mean first shock success rate will be 93%. A clinically meaningful difference in first full output shock efficacy is 5%. A total study sample size of 544 patients (272 in each group) is needed to provide a power of 80% to reject the null hypothesis (a difference in efficacy of < 5%).

13. SAFETY MANAGEMENT

13.1 Regulatory and Ethical Considerations

13.1.1 Data and Safety Monitoring Plan

The Inova PI will monitor and review the study progress, participant safety, and the accuracy and security of the data. This will be a minimal risk study. The risks of participation are limited to unexpected loss of confidential PHI.

13.1.1.1 Communication Plan

This is a single center study. There are no collaborating institutions.

13.1.2 Risk Assessment

The research interventions include on-label use of two FDA approved defibrillators for DCCV of AF. These procedures include the risks of asystole, arrhythmia, stroke and skin burn or irritation. These risks are present whether or not these procedures are performed as part of a research study. The only risk associated with participation in the study is accidental loss of PHI. This risk will be minimized by temporarily storing the paper case report forms in secure locations and long-term storage of all data in a REDCAP database with shredding of the paper case report forms.

13.1.3 Potential Benefits of Trial Participation

There is no benefit to individual participants in the research study,

however, the study results will inform IHVI and all other hospitals if there are clinical differences in efficacy or safety of the two commercially available defibrillators. These findings may improve the likelihood of successful and safe DCCV for our future patients as well as patients cared for in hospitals around the world. The results will be reported on clinicaltrials.gov where they will be available to the device manufacturers and the FDA. The results will also be published in a peer reviewed manuscript and presented at a major society meeting.

13.1.4 Risk-Benefit Assessment

Overall risks to research participants are minimal and limited to potential loss of PHI. The benefit of participation is improvement in our knowledge of the mechanism of cardioversion and improvement in the safety and efficacy of this commonly performed procedure. Because the benefits of the study far outweigh the minimal risks, we are justified in pursuing the study.

13.2 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

13.2.1 Adverse Events Reporting

Since the study procedures are not greater than minimal risk, significant adverse events (SAEs) are not expected. If any unanticipated problems related to the research involving risks to participants or others happen during this study (including SAEs), they will be reported to the IRB in accordance with Policy – Reporting of Adverse Events, Unanticipated Problems and Protocol Violations, ORI 11.16. AEs that do not meet prompt reporting requirements will be summarized in the narrative or other format and will be tracked and documented internally by the study team but not submitted to the IRB.

The investigator will comply with the requirements of ORI policy and of the reviewing IRB of record for the reporting of protocol deviations, adverse events, and unanticipated problems presenting risk to participants or others (UPIRSOs) to the IRB. If the Inova IRB is not the IRB of record, the Investigator must still submit prompt reports of any potential serious or continuing non-compliance or UPIRSOs to the Inova IRB via the electronic submission system consistent with ORI policy.

13.2.2 Follow-Up Report to and from IRB

The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable

14. PARTICIPANT COMPENSATION AND REPORTS

14.1 Participant Compensation: Not Applicable

14.2 Reporting Events to Participants

14.2.1 Adverse Events Not Applicable

14.3 Study Results and Incidental Findings

14.3.1 Study Results- Study results will be published in peer reviewed manuscripts, society meetings, and on clinicaltrials.gov where they can be seen by study participants.

14.3.2 Incidental Findings Not applicable

15. ECONOMIC BURDENS AND COMPENSATION / INCENTIVE

15.1 Foreseeable Costs

15.1.1 Economic Burden to Participants

We expect no financial or economic burden for the participants

15.2 Payments / Reimbursements

Not applicable

15.2.1 Reimbursement for Travel, Parking and Meals Not applicable

15.2.2 Payments to Parent/LAR for the Time and Inconvenience (i.e. compensation) Not applicable

15.2.3 Payments to Participants for Time, Effort and Inconvenience (i.e. compensation Not applicable

15.2.4 Gifts Not applicable

16. CONSENT PROCESS

16.1 Informed Consent- We have applied for a waiver of documentation of informed consent and alteration of HIPPA

16.1.1 Waiver of documentation of Informed Consent- Please see the completed request within the electronic submission system. Patients will be provided an opt-out information sheet about the study but will not be asked to sign an informed consent form.

16.2 HIPAA Research Authorization(s)

The Inova Health System uses a stand-alone HIPAA Research Authorization that is compliant with federal, state and institutional Privacy rules and regulations.

16.2.1 Alteration of HIPAA Authorization- We have submitted an alteration of

HIPPA authorization. Please see the request for alteration of HIPPA authorization within the electronic submission system. Patients will be given an information sheet discussing this alteration of HIPPA authorization with the ability to opt-out of participation if desired.

16.3 Safeguards for Vulnerable Populations

16.3.1 Cognitively Impaired Individuals- Will not be enrolled in the study.

16.3.2 Pediatric Participants- Children will not participate in the study

16.3.3 Individuals with Limited English Proficiency- Will be enrolled in the study using a translated information sheet. This will be submitted as an amendment and patients with limited English proficiency will not be enrolled until this is approved.

16.3.4 Adults Unable to Consent- Since consent will not be required, adults unable to consent will be enrolled.

16.4 Documentation of Consent:A waiver of documentation of consent has been submitted.

16.5 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

Participants may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to reasons listed below. The Investigator or Sponsor may also withdraw participants who violate the study plan, or to protect the participant for reasons of safety or for administrative reasons. It will be documented whether each participant completes the study. If the Investigator becomes aware of any serious, related adverse events after the participant completes or withdraws from the study, the participants will be communicated based on the IRB's directions.

16.6 Discontinuation of Study Intervention

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

16.7 Participant Discontinuation/Withdrawal from the Study

Participant may voluntarily withdraw from the study or discontinue the study intervention at any time.

Participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy of study endpoints

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

16.7.1 Significant study intervention non-compliance.

16.7.2 Any Clinical Adverse Event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

16.7.3 Disease progression which requires discontinuation of the study intervention.

16.7.4 If the participation meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

16.7.5 Participant unable to receive DCCV on the scheduled date/time.

The reason for participant discontinuation or withdrawal from the study will be recorded on the paper Case Report Form (CRF).

17. RECORDINGS

NA

18. IRB REVIEW HISTORY

NA

19. COORDINATING CENTER FOR MULTI-SITE STUDIES

19.1 Participating Sites

NA

19.2 Description of Collecting Sites

NA

19.3 Study-Wide Number of Participants

560

19.4 Communication to Participating Sites

20. REFERENCES / BIBLIOGRAPHY

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