Study Title:	Investigating the Efficacy of Chest Pressure for Direct Current Cardioversion in Atrial Fibrillation: A Randomised Control Trial (Pressure-AF)
Protocol Number:	2020/ETH02116
CTN Number:	ACTRN12620001028998p
Intervention	Chest Pressure
Indication:	Direct Current Cardioversion for Atrial Fibrillation
Study Design:	Investigator-initiated
Version:	1.4
Date:	24th November 2020

PROTOCOL SYNOPSIS

Study Title:	Investigating the Efficacy of Chest Pressure for Direct Current Cardioversion in Atrial Fibrillation: A Randomised Control Trial (Pressure-AF)
Study Period:	2021-2023
Hypothesis	The routine use of manual chest pressure for direct current cardioversion in atrial fibrillation will result in decreased energy requirements and will prove safe for patient and proceduralist.
Objectives:	Primary objective: • To assess the efficacy of chest pressure for direct current cardioversion in atrial fibrillation. The secondary objectives are: • To confirm safety and tolerability of chest pressure for patient and proceduralist
Study Plan	This is a multi-centre, randomised, single blinded trial of chest pressure for direct current cardioversion in atrial fibrillation. Participants will be screened from all participants referred for cardioversion for atrial fibrillation aged over 18 years of age. Randomisation will occur after consent is obtained and on enrolment into the study. Participants will be randomised to an initial strategy of chest pressure (intervention) or a strategy of chest pressure only if refractory to cardioversion without pressure (control).

Number of participants:	It is planned that 308 participants will be randomised in a 1:1 ratio to one of two treatment arms:
	• 154 will undergo standard direct current cardioversion.
	  ➢ 1 shock – 150 Joules without chest pressure
	  ➢ 1 shock – 200 Joules without chest pressure
	  ➢ 1 shock – 360 joules without chest pressure
	  ➢ 1 shock – 360 joules with chest pressure
	• 154 will undergo an initial strategy of chest pressure.
	  ➢ 1 shock – 150 Joules with chest pressure
	  ➢ 1 shock – 200 Joules with chest pressure
	  ➢ 1 shock – 360 Joules with chest pressure
	  ➢ 1 shock – 360 joules with chest pressure

Key inclusion	Participants who:

criteria:	• Aged over 18 years of age. • Have Atrial Fibrillation. • Are referred for direct current cardioversion for atrial fibrillation. • Three weeks of therapeutic anti-coagulation prior to cardioversion or transoesophageal echocardiography excluding left atrial appendage thrombus.
Key exclusion criteria:	Participants with: • Pregnant or breastfeeding females. • Inability to provide informed consent. • Other atrial tachyarrhythmias (atrial flutter of multifocal atrial tachycardia) • Medical comorbidity where anticoagulation is contra-indicated
Test strategy:	Direct current cardioversion for atrial fibrillation with and without chest pressure as the initial strategy.
Duration of study per participant:	Day of procedure only.
Criteria for evaluation:	<u>Primary efficacy endpoints</u> • Total joules provided during encounter. <u>Secondary efficacy endpoints:</u> • Success of first shock for reversion to sinus rhythm. • Transthoracic impedance at the time of shock. • Sinus rhythm at post cardioversion ECG <u>Safety and Tolerability Endpoints</u> • Patient chest pain post cardioversion (Ordinal Scale 0-10). • Incidence of shock provided to proceduralist.
Statistical methods and analyses:	<u>Analysis Sets</u> • Full analysis set (FAS) Intention to Treat (ITT) Protocol: All participants randomised into the study. Participants will be analysed according to the intervention to which they were randomised. Efficacy analyses performed in the FAS are considered supportive of analyses performed in the PP set. • Per-protocol (PP) set: All participants from the ITT population who completed the study in compliance with the protocol and who reported no major violation of the study protocol. Participants will be analysed according to the intervention which they received. The final decision to exclude a participant from the PP set will be taken during a blinded data

review meeting before database lock. Efficacy analyses performed in the PP set are considered supportive of analyses performed in the ITT set.

Sample Size

A retrospective review of 12 months of direct current cardioversions was performed at our centre. The mean energy provided during an encounter was 280 ± 188 Joules. Assuming a mean reduction of 60 joules in energy in the intervention group (one third of the standard deviation), a total of 308 patients (154 in each arm) would need to be recruited for an alpha of 0.05 and power of 0.8. This has been discussed and confirmed with statisticians at the Hunter Medical Research Institute.

Statistical Analyses

Continuous variables will be reported as mean ± standard deviation or as median and percentiles if appropriate. Normally distributed variables will be compared using the paired Student's t-test. Otherwise comparisons between both the groups will be performed using the Mann–Whitney U test. Categorical variables will be stated as absolute and relative frequencies and compared using the $\chi 2$ test. All tests are two-tailed. A P-value of <0.05 will be considered as statistically significant.

Sensitivity analyses of the primary endpoint will be performed in the FAS to assess the impact of missing data on the robustness of the primary analysis. The primary analysis will also be repeated in the PP set.

The following secondary endpoints will be analysed and summarised using the methods described for the primary endpoint:

- Success of first shock for reversion to sinus rhythm.
- Average transthoracic impedance.
- Chest pain post procedure – ordinal 0-10 scale.
- Shock provided to the provider.

Successful cardioversion is defined as sinus rhythm 1 minute after cardioversion.

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LIST OF ACRONYMS AND ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin II Receptor Blocker
AST	aspartate aminotransferase
AUC_{inf}	Area under (concentration-time) curve to infinity
AUC_{last}	Area under (concentration-time) curve to last time-point
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
C	Celsius
CEC	Clinical Endpoints Committee
CEO	Chief Executive Officer
C_{ave}	Average plasma concentration over 24 hours
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CNS	Central nervous system
COX-2	cyclooxygenase-2
CPK	creatine phosphokinase
CRF	Case Report Form
DCC	Direct Current Cardioversion
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ESV	End systolic volume
F	Fahrenheit
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GRAS	Generally Regarded as Safe
HDPE	High density polyethylene
hERG	human ether-à-go-go-related gene
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl methylcellulose
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee

IP	Investigational product
ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
LDH	lactate dehydrogenase
LS Mean	Least Squares Mean
LV	Left ventricular
LVEDVi	Left ventricular end diastolic volume (indexed)
LVEF	Left ventricular ejection fraction
LVESVi	Left ventricular end systolic volume (indexed)
MACCE	Major cardiac and cerebrovascular events
MAD	Multiple ascending dose
mg	milligram
MI	Myocardial infarction
min	Minute
mITT	Modified Intent to Treat
mL	Millilitre
MMRM	mixed model repeated measures
MTD	maximum tolerated dose
nM	nanomols
NOAEL	No observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	Brain natriuretic peptide type B
NYHA	New York Heart Association
PAD	Pharmacologically active dose
PCEs	polychromatic erythrocytes
PCI	Percutaneous coronary intervention
pg	picogram
PI	Principal Investigator
PICF	Participant Information and Consent Form
PK	Pharmacokinetic
PP	Per Protocol
PPP	PharmPackPro
PSA	Prostate specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QTc	Corrected QT interval
QTcB	Bazzet's corrected QT interval
RBC	Red blood cell
SAD	single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SOP	Standard Operating Procedure
SRM	Study Reference Manual
STEMI	ST elevation myocardial infarction

$T_{1/2}$	Terminal elimination half-life
TK	Toxicokinetic
T_{max}	Time to maximal concentration
ULN	Upper limit of normal
uM	micromol
WBC	White blood cell
WOCBP	Woman of child-bearing potential

1. BACKGROUND AND RATIONALE

1.1. ATRIAL FIBRILLATION AND DIRECT CURRENT CARDIOVERSION

Chest pressure during direct current cardioversion for atrial fibrillation is often utilised when patients fail regular cardioversion, often as standard of care. We hypothesise that the routine use of chest pressure for direct current cardioversion will be safe and reduce energy use compared to direct current cardioversion without pressure for atrial fibrillation.

There are numerous potential advantages to identifying the benefit of chest pressure for direct current cardioversion. This would result in potential improved cardioversion success, decreased energy use, potentially lower post procedural pain and decreased duration of anaesthetisation for patients.

1.2. CLINICAL STUDIES OF DIRECT CURRENT CARDIOVERSION FOR ATRIAL FIBRILLATION

There have been numerous studies, mostly observational and retrospective, examining the success of cardioversion in atrial fibrillation, however none have examined the role of chest pressure in cardioversion success. (1, 2)

1.2.1. Safety

Direct current cardioversion requires anaesthetic support for sedation as well as three weeks of therapeutic anticoagulation prior. The major complications from direct current cardioversion including ischaemic stroke (<1%) and ventricular arrhythmias due to non-synchronised shock. (2)

1.2.2. Efficacy

A retrospective review of 12 months of cardioversions for atrial fibrillation at our centre was performed, with a total of 147 patients. The success of the first and last shocks for reversion of sinus rhythm were 71% and 87% respectively.

1.3. STUDY RATIONALE

The success of direct current cardioversion relies on the delivery of energy to the heart. Most of the energy is displaced laterally across the chest wall, with only a small proportion delivered to the heart. (2) Chest pressure reduces transthoracic resistance by 25%, increasing cardiac energy delivery. (3) Therefore, routine chest compression may improve the success rate and decrease overall energy use.

Biphasic energy will be utilised due to reported increased efficacy and less myocardial stunning compared to monophasic cardioversion. (4, 5) Three weeks of therapeutic anticoagulation will be required prior to cardioversion in keeping with international guidelines or transoesophageal echocardiography excluding left atrial appendage thrombus. (6) 150 joules shall be used as the initial energy given guideline recommendations for starting energies between 100 and 200 joules. (7, 8) Cardioversion will be timed to end-expiration to maximally reduce transthoracic impedance. (9)

2. STUDY OBJECTIVES

To evaluate the efficacy of chest pressure for direct current cardioversion in AF.

2.1. PRIMARY OBJECTIVE

To assess the efficacy of chest pressure for direct current cardioversion in atrial fibrillation.

2.2. SECONDARY OBJECTIVES

To confirm safety and tolerability of chest pressure for the proceduralist

2.3. OVERALL TRIAL DESIGN

This is a multi-centre, randomised controlled study to assess the efficacy, and safety of direct current cardioversion for atrial fibrillation. Participants will be screened on the day of direct current cardioversion. Consenting participants will be randomised 1:1 to have an initial strategy of chest pressure with cardioversion or an initial cardioversion without chest pressure.

2.4. NUMBER OF PARTICPANTS

It is planned that approximately 308 adult participants aged over 18 years (inclusive) will participate in the study.

2.5. STUDY PERIOD/DURATION OF PARTICIPANT PARTICIPATION

The duration of the study for each participant is the day of the procedure.

It is anticipated that recruitment will take approximately 24 months. The study period is expected to be 2021-2023.

2.6. PARTICIPANT SELECTION AND WITHDRAWAL

2.6.1. Trial selection record

Investigators must keep a record of participants who were considered for the study but were not enrolled.

2.6.2. General considerations

Only participants who meet all the inclusion and none of the exclusion criteria will be eligible to participate in the study.

2.6.3. Inclusion criteria

1. Aged over 18 years of age.
2. Have Atrial Fibrillation.
3. Are referred for direct current cardioversion for atrial fibrillation.
4. Three weeks of therapeutic anti-coagulation prior to cardioversion or transoesophageal echocardiography excluding left atrial appendage thrombus.

2.6.4. Exclusion criteria

- Pregnant or breastfeeding females.
- Inability to provide informed consent.
- Medical comorbidity where anticoagulation is contra-indicated.

2.6.5. Concomitant Medications

Any medications taken must be documented in the participant notes. This record should include the drug name, the dose and frequency, route of administration and the indication.

2.6.6. Withdrawal of Pariticpants from Study

Participants can terminate their study participation at any time and without giving a reason, without prejudice to further treatment. Participants who discontinue from the trial should always be asked about the reason(s) for their discontinuation and about the presence of any AEs. AEs should be followed up until resolved or stable and determined to be chronic.

The Investigator or treating physician can exclude a participant from continuing in the trial.

Possible reasons for discontinuing a participant may include:

- Participant withdrawal of consent.
- Any unacceptable AEs, in the judgement of the Investigator.
- Participant non-compliance with the protocol.

2.7. STUDY TREATMENTS

2.7.1. Description of the control arm

Patients in the control arm will receive sequential shocks of 150J without pressure, 200J without pressure,360J without pressure and 360J with chest pressure until cardioversion success or four shocks have been provided. The cardioversion will be performed under intravenous sedation guided by an anaesthetist (Propofol ± midazolam weight-based dosing and titrated to effect).

2.7.2. Description of intervention arm

Patients in the intervention arm will receive sequential shocks of 150J with pressure, 200J with pressure and two shocks at 360J with pressure until cardioversion success or four shocks have been provided. The cardioversion will be performed under intravenous sedation guided by an anaesthetist (Propofol ± midazolam weight-based dosing and titrated to effect).

2.7.3. Chest pressure standardisation

The application of standardised chest pressure is needed to ensure consistency of the intervention. A review of chest pressure provided by Cardiology Advanced Trainees (the proceduralists for the intervention) was performed. Of thirty-six measurements, on a single set of scales, between four advanced trainees (8 measurements each), an average of 25.5±2.6 kilograms of chest pressure was provided.

2.7.4. Anaesthetic Protocol for DC Cardioversion

Anaesthetic agents have potential pro and antiarrhythmic effects. (9, 10) As such, the standardisation of anaesthetic provision will be necessary for internal validity of the trial. Generally, the application propofol and midazolam is routinely used for elective direct current cardioversion. During this trial, the weight-based dosing of propofol +/- midazolam, titrated to effect, will be used for sedation purposes.

2.7.5. Method of assigning participants to treatment group

Participant eligibility will be established before randomisation. Eligible participants who consent to involvement will be assigned to either the control or intervention arm in a 1:1 ratio. Patients will be

randomised via a randomisation app. This app, given to all researchers, will provide synchronised information about patient allocations.

3. STUDY PROCEDURES

3.1. PARTICIPANT INFORMATION

The Investigator must provide adequate information regarding the study conduct and obtain written informed consent from the participant before any tests or investigations outlined in the study protocol are carried out.

3.2. DAY OF CARDIOVERSION

On the day of cardioversion the following will be performed:

- Review eligibility criteria.
- Record participant medical history and medications.
- Record the height and weight of the patient.
- Vital signs (see Section 5.2).
- 12-lead ECG.
- Written informed consent.
- Upon confirmation of eligibility and consent to proceed, participants will be randomised.

The protocol for DC cardioversion (control or intervention) will then be performed based on randomisation. After the DC cardioversion is completed, the following will be performed:

- Chest pain 30 minutes post procedure will be recorded (0-10 ordinal scale)
- Record of post-procedural complications:
    - shock provided to proceduralist

4. TRIAL ENDPOINTS

4.1. EFFICACY ENDPOINTS

4.1.1. Primary

- Total joules provided to patient.

4.1.2. Secondary

- First shock success in reversion to sinus rhythm
- Transthoracic impedance at the time of shock
- Sinus rhythm at post cardioversion ECG

4.2. SAFETY AND TOLERABILITY ENDPOINTS

- Chest pain 30 minutes post procedure.
- Shock to proceduralist

5. TRIAL MEASUREMENTS

5.1. EFFICACY

Total joules provided during a patient encounter will be measured. First shock success percentage will be compared between groups. Transthoracic impedance with each shock (a measurement provided by the defibrillator) will also be recorded.

5.2. SAFETY AND TOLERABILITY

Safety will be assessed by recording of AEs, and MACCE.

- Participants will be questioned and monitored throughout in-patient stag with regard to any AEs they may have experienced. See Section 6 for further details on recording AEs.
- Vital signs will be measured after the participant has been supine for 5 minutes and will include blood pressure (BP), pulse rate, respiratory rate and temperature.
- Measurement of chest pain 30 minutes post procedure will be elicited by medical staff (Ordinal scale of 0-10).
- Shock provided to proceduralist will be documented.

6. ADVERSE EVENTS

The definitions of AEs and SAEs are given below. It is extremely important that all staff involved in the trial are familiar with the content of this section. The PI is responsible for ensuring this.

6.1. ADVERSE EVENT DEFINITIONS

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered the study treatment and which does not necessarily have a causal relationship with this strategy. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

Laboratory reference ranges are defined by upper or lower limits of parameters of the laboratory. The Investigator should ensure that each parameter out of the normal range is assessed for clinical significance and potential for being an AE. It is at the discretion of the Investigator to document any change in laboratory result as an AE if he considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

The participant must be instructed to inform the Investigator about all AEs and these must be documented in the participant records and Case Report Form (CRF) together with their intensity;

- Severe are those AEs which make normal daily routine impossible.
- Moderate AEs impact the normal daily routine
- Mild AEs do not impact normal daily routine.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilised for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 6.2.

The Investigator must assign causality to each adverse event in relation to based on the following scale:

- **Not related:** AE for which there is evidence of another explanation, e.g. the adverse event is obviously explained by the participant's disease(s), is in accordance with the known effect of a concomitant medication, or has occurred prior to commencement of ILR follow-up period.
- **Unlikely related:** AE with a time to ILR follow-up commencement that makes a relationship improbable (but not impossible), and disease or other drugs provide plausible explanations.
- **Possibly related:** AE with a reasonable time relationship to ILR follow-up commencement, but which could also be explained by disease or other drugs.
- **Probably related:** AE with reasonable time relationship to ILR follow-up commencement that is unlikely to be attributed to disease or other drugs.
- **Definitely related:** AE with plausible time relationship to ILR follow-up commencement which cannot be explained by disease or other drugs.

All AEs must be documented by the Investigator, regardless of causality.

Expected AEs are defined as all AEs stated in the IB. If an AE has not been previously reported (including type, degree, or frequency) in the IB, it is an unexpected adverse event.

If an AE leads to premature discontinuation of the study, the appropriate pages of the CRF must be completed.

6.2. SERIOUS ADVERSE EVENTS (SAES)

An AE shall be classified as serious if it:

- Results in death.
- Is life-threatening.

  Life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires in-patient hospitalisation or prolongation of existing hospitalisation.

  Hospitalisation is defined as in-patient admission or care regardless of duration.

  Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Elective surgery, hospitalisation for social reasons (with no causal AE), or hospital admissions and/or surgical operations planned before or during this study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

  This includes events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above.

6.3. RECORDING OF ADVERSE EVENTS

AEs will be captured from the time of informed consent until the discharge. Participants will be asked whether they have experienced any AEs. If a participant has concern over ongoing symptoms or events, they are encouraged to see their local GP or the emergency department to address these concerns.

It is preferable that AEs are reported as diagnoses if one is able to be made, rather than individual signs and symptoms. The AE description, start and stop dates, intensity, causality and outcome must be recorded, as well as any actions taken.

Unless a diagnosis is made, or signs and symptoms are present, laboratory values or vital signs abnormalities should only be reported as AEs if they cause the participant to discontinue from the trial, the investigator feels it is clinically significant, or they meet a criterion for a SAE.

6.4. REPORTING OF SERIOUS ADVERSE EVENTS

Follow-up information on SAEs must be reported by the investigational site within 24 hours. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

All SAEs will be recorded in the participant records and the CRF.

The investigator must notify their Independent Ethics Committee (IEC) of any SAEs occurring at their site, within the time specified by the IEC.

6.5. FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All AEs and all SAEs must be followed by the Investigator until resolution, until the AE stabilises or is recognised as a permanent condition by the Investigator, or until the participant is lost to follow up, whichever comes first. Follow-up investigations may be necessary according to the Investigator's medical judgement.

7. DATA MANAGEMENT

Data collection and entry into the CRF will be completed by authorised study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorised study site personnel prior to the study being initiated and any data being entered into the system for any study participants.

All data must be entered in English. The CRFs should always reflect the latest observations on the participants in the trial; therefore, the CRFs are to be completed as soon as possible after the participant's visit. The Investigator must verify that all data entries in the CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the CRF. The Investigator will be required to sign off on the clinical data.

8. STATISTICAL ANALYSIS

8.1. INTERIM ANALYSIS

After 12 months of patient enrolment, the statistical team will review recruitment and adverse events. 30% recruitment of the total sample size (308) will be required after 12 months in order to continue the trial. If a significant difference in adverse events is detected, the appropriateness of ongoing recruitment will be discussed with the local research ethics committee. Primary and secondary efficacy outcomes will not be assessed at this time to reduce the potential for bias.

8.2. STASTICAL ANALYSIS PLAN

Continuous variables will be reported as mean ± standard deviation or as median and percentiles if appropriate. Normally distributed variables will be compared using the paired Student's t-test. Otherwise comparisons between both the groups will be performed using the Mann–Whitney U test. Categorical variables will be stated as absolute and relative frequencies and compared using the $\chi 2$ test. All tests are two-tailed. A P-value of <0.05 will be considered as statistically significant.

8.3. ANALYSIS SETS

The following sets will be used for the statistical analyses:

Intention to treat full analysis set (ITT FAS): All participants randomised into the study will be included in the ITT FAS. Participants will be analysed according to the intervention to which they were randomised. Primary and secondary outcomes will be analysed based on the FAS.

Per-protocol (PP) set: All participants from the ITT FAS population who completed the study in compliance with the protocol. Participants will be analysed according to the intervention which they received. The final decision to exclude a participant from the PP set will be taken during a blinded data review meeting before database lock. Efficacy analyses performed in the PP set are considered supportive of analyses performed in the ITT set.

8.4. PRE-SPECIFIED POST-HOC ANALYSIS

Post-hoc analyses will be performed based on the following variables:

- Body Mass Index (greater and less than 30 ,40 and 50)
- Left Atrial Size (indexed left atrial size/volume)
- Age (younger and older than 40, 60,and 80 years of age)
- Anti-arrhythmic therapy (Beta Blockers, Sotalol, Flecainide and Amiodarone)

8.5. DATA ANALYSIS CONSIDERATIONS

All efficacy and safety data will be listed and summarised using descriptive statistics by treatment group. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include means, medians, standard deviation and minimum and maximum values. Where possible, data from participants who withdraw prematurely from the study will be included in any analysis.

All statements of statistical significance will be based on a two-sided test at the 5% level of significance, unless stated otherwise. If the study is prematurely discontinued, all available data will be listed and a review will be carried out to determine which statistical analyses are considered appropriate.

8.6. SAFETY DATA

8.6.1. Adverse events

AE data will be listed individually and incidence of AEs summarised by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE, based on preferred terminology defined by Medical Dictionary for Regulatory Activities (MedDRA; Version 13.1, or later), will be counted only once for a given participant. A summary of the number and percent of participants with the following treatment emergent AEs will be displayed by treatment groups:

- All AEs
- Intervention-related AEs
- Severe AEs
- SAEs
- AEs leading to discontinuation of the study or cross-over.

8.6.2. Other safety measures

Continuous variables will be summarised along with the change from baseline at each time point by treatment group. Other variables will be summarised as appropriate to the data.

9. TRIAL MANAGEMENT

9.1. QUALITY CONTROL AND QUALITY ASSURANCE

9.1.1. Monitoring

Study monitoring will be performed in accordance with applicable regulations, ICH Good Clinical Practice (GCP), and study site Standard Operating Procedures (SOPs).

Before the start of the trial, the PI will ensure facilities are adequate and discuss responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements.

During the trial, the PI will regularly monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support as needed.

9.2. TRAINING OF STAFF

Everyone involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.

The PI will maintain records of all individuals involved in the trial at their site. The PI will ensure that appropriate training relevant to the trial is given to all these staff, and that they will receive any new information relevant to the performance of this trial in a timely manner.

9.3. CHANGES TO THE PROTOCOL

If it is necessary for the trial protocol to be amended, the amended protocol must be approved by the IEC, unless the immediate safety of participants is involved.

If a protocol amendment requires a change to the PICF, approval of the revised PICF by the IEC is required before the revised form can be used.

9.4. TRIAL TIMETABLE AND TERMINATION

The planned start date for this trial is March 2021. The proposed completion date is in March 2023.

9.5. ETHICS REVIEW

The protocol and the PICF will be submitted for approval to the HREC and must be approved or given a favourable opinion in writing as appropriate.

Any amendment to the protocol will be sent to the HREC. No deviations from or changes to the protocol will be implemented without documented approval/favourable opinion from the HREC of an amendment, except where necessary to eliminate an immediate hazard to a trial participant, or when the changes involve only logistical or administrative aspects of the trial.

The deviations from or changes to the protocol which were implemented to eliminate an immediate hazard to a trial participant and the proposed amendment, if appropriate, should be submitted to the HREC for review and approval as soon as possible.

The PI must submit progress reports to the HREC according to local regulations and guidelines. The PI must also provide the IEC with any reports of SAEs from the trial site in accordance with the IEC requirements and timelines.

9.6. ETHICAL CONDUCT OF THE STUDY

The trial will be performed in accordance with the ethical principles in the Guidelines of the World Medical Association's Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), ICH GCP, the NHMRC's National Statement on Ethical Conduct in Research the approved study protocol, and applicable regulatory requirements.

9.7. INSURANCE AND LIABILITY

As an investigator-initiated trial conducted in a NSW Public Health Organisation, this will be covered by Treasury Managed Funds.

9.8. PARTICIPANT INFORMATION AND INFORMED CONSENT

The PI at each centre will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and potential benefits of the trial. Participants must also be notified that they are free to discontinue from the trial at any time. The participant should be given the opportunity to ask questions and should be allowed time to consider the information provided.

The Participant's signed and dated informed consent must be obtained before conducting any procedure specifically for the trial. The site investigator must store the original, signed PICF. A copy of the signed and dated PICF must be given to the participant

9.9. DATA PROTECTION

The PICF will explain that trial data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. Participants in this database will be identified by participant ID number only. The PICF will also explain that for data verification purposes IECs or sites may require direct access to parts of the hospital or site records relevant to the trial, including personal participant information.

9.10. ARCHIVING

The PI is responsible for the archiving of the trial records for their site. Trial records include the participant files as well as the source data, the Investigator Site File, and other study documents. Trial records must be archived for at least 15 years.

However, these documents should be retained for a longer period if specified by regulatory requirements.

If the PI leaves the investigational site for whatever reason, the responsibility for all study related records must be transferred to another person at the site.

9.11. PUBLICATION POLICY

An investigator may publish any data related to this study (poster, abstract, paper, slide presentation, etc.)

10. REFERENCES

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