Statistical Analytical Plan

Study Title:	**Study to evaLuate the EfficAcy and Safety of CardiolRx™ in PatieNts with COVID-19 and Cardiovascular DisEase or Risk Factors** A double-blind, placebo-controlled trial (**LANCER**)
Sponsor:	Cardiol Therapeutics Inc. 602 - 2265 Upper Middle Road East Oakville, ON, L6H 0G5, Canada
Trial Statistician:	Stuart J. Pocock, BSc., MSc., PhD
Protocol Prepared by:	Cardiol Therapeutics Inc.
Document type:	Statistical Analytical Plan
Protocol number:	CARDIOL 100-03
Protocol version:	Amendment 3
Protocol date:	September 23, 2021
Document version:	1.0
Document Release date:	January 19, 2023

Signature Page for Sponsor

Study to evaluate the Efficacy and Safety of CardiolRx™ in Patients with COVID-19 and Cardiovascular Disease or Risk Factors:
A double-blind, placebo-controlled trial (LANCER)
Statistical Analytical Plan

Reviewed and Approved by:

DocuSigned by:
Andrea Parker
Signer Name: Andrea Parker
Signing Reason: I approve this document
Signing Time: 24-Jan-2023 | 10:05:49 PST
67ACA71D7793463992E8671996F70B01

24-Jan-2023 | 10:05:56 PST

Andrea B. Parker, MSc., PhD
Director, Clinical Affairs

Date

DocuSigned by:
Signer Name: Andrew Hamer
Signing Reason: I approve this document
Signing Time: 24-Jan-2023 | 12:03:11 PST
4B9572D0C730410A90A26CB6E4EF4E75

24-Jan-2023 | 12:03:15 PST

Andrew Hamer, MD
Chief Medical Officer

Date

DocuSigned by:
Stuart Pocock
Signer Name: Stuart Pocock
Signing Reason: I approve this document
Signing Time: 25-Jan-2023 | 02:58:02 PST
F93DFA76DBAB416694E07C33050AFAED

25-Jan-2023 | 02:58:12 PST

Stuart J. Pocock, BSc., MSc., PhD
Trial Statistician

Date

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ACE	Angiotensin Converting Enzyme
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ARB	Angiotensin Receptor Blocker
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area under the curve
BNP	Brain natriuretic peptide
CEC	Clinical Endpoint Adjudication committee
CMR	Cardiac magnetic resonance imaging
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECV	Extracellular volume
eGFR	Estimated Glomerular filtration rate
HF	Heart failure
hs-CRP	High sensitivity-C-reactive protein
hs-troponin	High sensitivity-troponin
ICU	Intensive Care Unit
INR	International normalized ratio
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEDV	Left ventricular end-diastolic volume

Abbreviation	Definition
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro b-type natriuretic peptide
PICQ	Patient impression of change questionnaire
PPP	Per protocol population
PT	Preferred Term
Q1 / Q3	First / third quartile
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard deviation
SD1	First study day
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TNF	Tumor necrosis factor
WHO	World Health Organization

2 INTRODUCTION

This document describes the Statistical Analysis Plan (SAP) for the CARDIOL 100-03 Protocol (Study to evaluate the Efficacy and Safety of CardiolRx™ in Patients with COVID-19 and Cardiovascular Disease or Risk Factors [LANCER]. This is a multi-center, double-blind, randomized, placebo-controlled, parallel group design, 1:1 randomization study. In total 422 patients will be randomized (1:1) to either CardiolRx™ or placebo.

The design and methods of the CARDIOL 100-03 study are described in detail in the study protocol Amendment 3, dated September 23, 2021. The criteria for evaluation of study results and the analysis populations are defined in section 10 of the study protocol and an outline of the statistical analysis plan may be found in section 11 of the same document. The purpose of this document is to describe the analyses that will be performed in accordance with the protocol in more detail.

As the study was terminated early an abbreviated set of reporting will be generated as described herein. This plan will be approved prior to the breaking of the study blind. Changes from the protocol are noted.

3 STUDY DESIGN

3.1 Randomization Methodology

Randomization will be accomplished by means of a web-based randomization system and will be stratified by center. The program used is Medidata Rave RTSM. The randomization schedule is generated by an unblinded statistician per the protocol requirements and loaded in the system.

The randomization sequence will be generated by random computerized sequence in blocks of 4.

3.2 Blinding

The treatment assignment is double-blinded and will not be known by the patients, the physician and clinical staff involved in the patient care.

The preparation and/or administration of the products will be done by designated personnel that are not involved in any other aspects of the trial.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an investigator for further treatment of the patient. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Efficacy

4.1.1 Primary Efficacy Objective

As stated in section 4.1.1 of the study protocol, the primary objective for efficacy of the CARDIOL 100-03 study is to evaluate the effect of CardiolRx™ on prevention of cardiovascular (CV) and COVID-19 complications in patients hospitalized for COVID-19.

4.1.2 Primary Efficacy Outcome

The primary composite endpoint in this study is to experience one of the following events during the first 28 days post randomization:

- All-cause mortality
- Requirement for intensive care unit (ICU) admission and/or ventilatory support due to COVID-19
- CV complications*:
  - heart failure (HF) or
  - acute myocardial infarction (AMI) or
  - Myocarditis or
  - new sustained or symptomatic arrhythmia or
  - stroke

*Outcome definitions can be found in Appendix 17.8 of the study protocol.

4.1.3 Secondary Efficacy Objectives

Secondary objectives include the improvement in other clinical parameters during 28 days post randomization.

4.1.4 Secondary Efficacy Parameters

Secondary efficacy parameters include:

-Win Ratio of Ordinal Outcome Scale endpoint:

1) not hospitalized and no limitations of activities

2) not hospitalized, with limitation of activities, home oxygen requirement, or both;

3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care

4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care

5) hospitalized, requiring any supplemental oxygen;

6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;

7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

8) MI or stroke diagnosed since randomization

9) death.

- Change in high sensitivity-troponin (hs-troponin) from baseline to peak elevation during the 28-day treatment period
- Change in Tumor Necrosis Factor (TNF)-alpha from baseline to peak elevation during the 28-day treatment period

4.1.5 Other Efficacy Parameters

Other efficacy parameters include:

- Percentage of patients developing any one of the primary endpoint components within 60 days post randomization
- CV mortality at 28 days post randomization
- Percentage of patients requiring dialysis within 28 days post randomization
- Win ratio of the Ordinal Outcome Scale endpoint within 60 days of randomization
- Patient Impression of Change Questionnaire (PICQ) at Day 28 and at Day 60
- Development of severe lymphopenia, defined as < 1000 cells/ microliter within 28 days post randomization
- Change in (elevation of) hs-troponin, NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) from baseline to Day 7 (AUC)
- Change from baseline to peak elevation of NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, IL-1 beta, IL-6, IL-10) during the 28-day treatment period
- Change from baseline to peak elevation of LDH during the 28-day treatment period
- Difference in cardiac magnetic resonance imaging (CMR) parameters: LVEF, LVEDV, LVESV, LAESV, ECV, GLS, LV mass, LGE extent and edema between the

two treatment groups after 4 weeks of study treatment (in a subset of patients at selected sites).

4.2 Safety

4.2.1 Safety Objective

The primary safety objective is to demonstrate that administration of CardiolRx™ in the proposed doses in this patient population is safe.

4.2.2 Safety Endpoints

The primary safety endpoint is the number of Serious Adverse Events (SAEs) and Adverse events (AEs) which occur during the 60-day study period.

The secondary safety endpoints include changes in C-SSRS, blood chemistry and hematology parameters (including lymphocyte count), ALT, AST, bilirubin, eGFR, creatinine, INR and QTc interval from Electrocardiogram (ECG) recordings at 5 hours post morning dose during 28 days post randomization.

4.3 Centralized Assessment of Endpoints

The Clinical Endpoint Adjudication Committee (CEC) will consist of at least three clinicians appointed by the Steering Committee. The CEC will classify all SAEs using pre-specified definitions described in the Event Classification manual, based on medical records and other documents. In addition, all endpoints will be verified by the CEC.

5 DEFINITION OF ANALYSIS POPULATIONS

The following analysis populations will be defined for this trial.

5.1 Intention-to-treat population (ITT)

The primary analyses will be performed on the ITT population. All patients who were randomized will be included in the ITT analyses.

5.2 Safety population (SAF)

The Safety Population (SAF) includes all subjects who received any study drug.

5.3 Per- protocol population (PPP)

The protocol defined a per-protocol population. However, due to the early termination of the study the PPP will not be generated.

5.4 Protocol Deviations

The sponsor, or designee, will be responsible for producing the final protocol deviation/violation file (formatted as an Excel file or SAS dataset). This file will be finalized prior to hard database lock. Protocol deviations will be reported in a data listing for all subjects in the ITT population.

6 STATISTICAL METHODS

6.1 Sample Size Justification

Assuming that 19% of patients qualifying for the study in the placebo group would develop one or more primary outcomes, a treatment effect of lowering the event rate by 50% (i.e. only 9.5% of patients treated with CardiolRx™ would experience a primary outcome event, a two-sided alpha of 0.05 and 80% power, 211 patients per group (422 in total) would be required.

The protocol contained information to consider an adjustment to the sample size. Due to the early termination of the study no sample size re-estimation will be performed.

6.2 General Statistical Methods and Data Handling

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

Due to the early termination of the study no statistical testing will be performed, with the exception of the bio- and inflammatory marker data (see Section 9). All summaries will be presented descriptively.

Listings will be sorted by treatment and subject ID unless specified otherwise.

6.2.1 Computing Environment

All analyses will be performed using SAS statistical software (Version 9.4 or later), unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization (WHO) Drug dictionary. Versions of dictionaries will be indicated in the relevant tables and listings.

6.2.2 Continuous Variables

For continuous variables, the mean, median, standard deviation (SD), first and third quartiles (Q1 and Q3), and minimum and maximum values will be presented. Means, medians and percentiles will be displayed to one more decimal place than the data, dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

6.2.3 Categorical Variables

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of subjects in the column header unless otherwise specified in the footnote. For each variable, all categories will be shown. Zero

frequencies (but not the percent) within a category will be presented. Percentages will be displayed with one decimal place

6.3 Interim Analysis

The protocol contained information to describe a formal interim analysis of the primary endpoint. Due to the early termination of the study no interim analysis will be performed.

6.4 Statistical Inference

Due to the early termination of the study no statistical testing will be performed, with the exception of the bio- and inflammatory marker data (see Section 9). All summaries will be presented descriptively.

6.4.1 Multiple Comparisons/Multiplicity

Due to the early termination of the study no adjustments for multiple comparisons are defined. All summaries will be presented descriptively.

6.4.2 Subpopulations

Section 11.5 of the protocol defined planned subgroups for exploration of the primary endpoint. Due to the early termination of the study no subgroups will be explored.

6.5 Handling of Unscheduled Visits

Visit data will be presented using nominal times as collected in the eCRF. Both scheduled and unscheduled post-baseline visits will be tabulated. Unscheduled visits will be presented as 'Visit.x.xx' (e.g. Visit 3.01).

6.6 Handling of Missing Information

6.6.1 Incomplete Calendar Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).
All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

Missing / Partial Start / Stop Date of Medical History, Adverse Events (AE)
Missing and partial start and stop date will be imputed for analysis purposes as follows.
Partial or missing stop date will be imputed as follows:
If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study regardless of whether remote or in-office visit.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the subject's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

6.6.2 Definition of First Study Day (SD1)

First study day (SD1) is defined as the date of first administration of study treatment.

6.6.3 Definition of Baseline

Baseline is defined as the last record or measure collected prior to the first dose of study medication.

If an assessment is collected on SD1 and either time of assessment or time of first dose is missing, then such assessment is considered as prior to the first dose. The exception to this rule are medications and AEs, which will be considered as concomitant or treatment-emergent, respectively.

6.6.4 Conversion factors

The following conversion factors will be used to convert days into months or years, or vice versa, if needed:

1 week = 7 days,

1 month = 30.4375 days, and
1 year = 365.25 days.

The following conversion factors will be used for height and weight:
1 cm = 0.39370 in, and
1 kg = 2.20462 lb.

6.6.5 Missing Data

All attempts will be made to minimize missing follow-up data. Data that are collected only at baseline will not be imputed.

Due to the early termination of the study no imputations for missing data will be applied with the exception of missing dates as described above. All summaries will be presented descriptively on available data.

7 DESCRIPTION OF STUDY POPULATION

7.1 Analysis Populations

The number of subjects meeting criteria for each analysis population will be tabulated.

7.2 Patient Disposition

The contribution of each centre to each of the two treatment arms and will be tabulated. The number of subjects attending each scheduled visit, discontinuing study medication prior to Day 28, terminating the study, reasons for early termination and time from randomization to study termination will be tabulated. The number of subjects considered screen failures and reason for screen failure will be tabulated. The number of subjects failing to meet any inclusion or exclusion criterion will be tabulated.

7.3 Baseline Characteristics

Baseline demographic data will be summarized.

7.3.1 Medical History

Tabulations of previous and ongoing conditions at screening will be presented by randomized treatment group and overall. Medical history marked as Ongoing status as 'No' or with an end date prior to the date of randomization is considered previous. Medical history marked as Ongoing status as 'Yes' or an end date on or after the date of randomization are considered as concurrent disease. Conditions will be presented by MedDRA primary system organ class and preferred term.

7.3.2 Concomitant medication

Prior medication refers to any medication that was stopped prior to the day of randomization. Concomitant medication refers to the new use or ongoing use of a medication at the randomization date up to and including the date of study termination.

Separate tabulations will be produced for prior or concomitant medications presented by randomized treatment group and overall for the Safety Analysis Set. Concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2.

Additionally, the number and percentage of subjects taking any medication in the following categories will be tabulated. Cardiovascular and non-cardiovascular treatments will also be tabulated separately.

- beta-blocker
- ACE-inhibitor
- diuretic

- insulin or angiotensin receptor blocker (ARB)
- antibiotic or antiviral Rx
- corticosteriod

7.3.3 Physical Examination

Physical examination results will be listed.

8 COMPLIANCE WITH STUDY MEDICATION AND DRUG ACCOUNTABILITY

For each visit the number of patients who were continued on any dose of study medication will be summarized.

In addition, drug accountability will be calculated for each visit.

Compliance at Visit x:

[(Total amount of IP dispensed at visit x [initial weight of all bottles dispensed] – Total amount of IP returned for bottles dispensed at visit x [weight of all bottles returned]) / Total amount of IP dispensed at visit x]*100.

9 EVALUATION OF EFFICACY AND SAFETY

9.1 Primary Analysis for Efficacy

The primary efficacy outcome is the percent of patients who experience one of the following events during the first 28 days:

- All-cause mortality
- Requirement for ICU admission and/or ventilatory support
- CV complications*:
  - HF or
  - AMI or
  - Myocarditis or
  - new sustained or symptomatic arrhythmia or
  - stroke

*Outcome definitions can be found in Appendix 17.8 of the study protocol.

9.1.1 Proportions of Subjects with an Event

All subjects who have met any condition of the composite outcome will be listed.

Due to the early termination of the study no analysis will be performed.

9.2 Secondary Efficacy Analyses

Due to the early termination of the study the Win Ratio of the Ordinal Outcome scale will not be generated. Ordinal outcome scale scores will be listed and summarized for each visit.

The change from baseline in each biomarker (hs-troponin, NT-proBNP, D-dimer) and inflammatory marker (hs-CRP, ferritin, IL-1 beta, IL-6, IL-10) over time will be summarized at each time point and graphically displayed. After review of the profiles over time, the following parameters may be calculated.

Emax 7	Maximum post-baseline change* (baseline-corrected change) up to the time of the Day 7 assessment; reported to 2 decimal places.
Emax 28	Maximum post-baseline change* (baseline-corrected change) up to the time of the Day 28 assessment; reported to 2 decimal places.
AUEC0-7	Area under the change from baseline curve from time zero to the Day 7

	assessment; calculated using the linear trapezoidal rule; reported to 3 significant figures.
AUEC0-28	Area under the change from baseline curve from time zero to the Day 28 assessment; calculated using the linear trapezoidal rule; reported to 3 significant figures.

*maximum post-baseline change will be positive for biomarkers that increase relative to baseline over the time interval; or negative for those that decrease relative to baseline.

Assumptions for AUEC calculation:

• Time points other than pre-dose will use actual time point instead of nominal time points. If actual assessment time is missing the nominal time will be used.
• Values missing at time points after baseline and prior to last time point in the interval will not be imputed.
• If data at last time point is missing, AUEC will be calculated up to latest non-missing time point.
• AUEC calculation will not include unscheduled and repeat measurements.

Comparison of each parameter between the two treatment groups using an ANCOVA with fixed factors for treatment and the baseline value as covariate will be performed.

9.3 Other Efficacy and Safety Analyses

9.3.1 Binary Outcomes

Subjects with an event will be listed for the following outcomes:

- any one of the primary endpoint components within 60 days post randomization
- CV mortality at 28 days post randomization

9.3.2 Columbia Suicide Severity Rating Scale (C-SSRS)

To monitor for the emergence of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at baseline and at Day 28.

The number of subjects experiencing suicidal Ideation or suicidal behavior will be summarized. Shift tables in relation to suicidal ideation and/or behavior from baseline to

Day 28 will be presented.

There will be no imputation of missing data for C-SSRS.

9.3.3 Patient Impression of Change Questionnaire (PICQ)

The patient will be asked to document how her/his overall status changed.

Data will be listed.

9.3.4 Laboratory Tests

For laboratory (Local Laboratory) data both scheduled and unscheduled post-baseline values will be tabulated. Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each parameter.

Each measurement (continuous data) will be classed as low(below normal range), normal (within normal range), or high (above normal range), based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each post Baseline visit will be presented.

As normal range for these assays may depend on gender, when applicable, data will be tabulated separately for men and women when applicable.

Additionally, a summary of targeted parameters against specified threshold limits will be presented.

9.3.5 Vital Signs

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each parameter.

9.3.6 ECG

Available standard ECG data will be tabulated by treatment group for each visit. Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for parameter. Each visit will be assessed as Normal/Abnormal and Clinically Significant/Not Clinically Significant. Shift tables in relation to the combined status from baseline to each post Baseline visit will be presented.

9.3.7 Chest X-Ray

Each visit will be assessed as Normal/Abnormal. Shift tables in relation to the combined status from baseline to each post Baseline visit will be presented.

9.3.8 Adverse Events

Adverse events are to be recorded throughout the study, beginning at the moment of informed consent. AEs will be coded using MedDRA and displayed in tables and listings by System Organ Class (SOC) and Preferred Term (PT).

Analyses of adverse events will be performed for those events that are considered treatment-emergent, where a treatment-emergent AE (TEAE) is defined as one that started, or worsened in severity or seriousness following the first dose of IMP. An AE with onset prior to the start of the administration of the first dose of study drug, or where the stop date is before the start of the administration of the first dose of study drug, or where the study drug was not started, will be considered as pre-study. In case the onset date is on the same day as the first dose of study drug and either the time of first dose or time of AE onset is missing, then AE is considered treatment-emergent.

AE intensity will be qualified as mild, moderate, or severe. Maximum severity will be assumed for an AE with missing severity. The relationship to the study drug will be qualified as related (including categories related, probably, possibly) or unrelated.
If the AE start date is missing or partial, the AE will be assigned to the appropriate period using available start date information and the stop date, if present as described above.

The following tables will be presented for AEs incidence and/or number of events will be reported as appropriate:

- Overall summary of AEs
- TEAEs by system organ class and preferred term
- Treatment related TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term and maximum severity
- TEAEs leading to study drug discontinuation by system organ class and preferred term
- Listing of AEs
- Listing of Serious TEAEs
- Listing of AESIs
- Listing of Deaths

Adverse event incidence is counted only once per system organ class and once per preferred term. The number and percent of subjects experiencing events are reported. Outputs reported at maximum severity show the highest severity reported by a patient per system organ class and preferred term.

10 CHANGES TO PLANNED ANALYSES

Due to the early termination of the study no inferential testing will be performed. All summaries will be presented descriptively. Limited scope reporting is described above.

11 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA

DocuSign

Certificate Of Completion

Envelope Id: 755DB66B11AA40E490520B482C3CE0E6
Status: Completed
Subject: Complete with DocuSign: 4010-Study-11.01.01-20230119-Statistical_Analysis_Plan_V1.0.docx
Source Envelope:
Document Pages: 25
Signatures: 3
Certificate Pages: 8
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Robin White
600 Park Offices Drive
Suite 200, Research Triangle Park
Durham, NC 27709
robin.white@worldwide.com
IP Address: 163.116.147.30

Record Tracking

Status: Original
24-Jan-2023 | 09:27
Holder: Robin White
robin.white@worldwide.com
Location: DocuSign

Signer Events	Signature	Timestamp
Andrea Parker andrea.parker@cardiolrx.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Andrea Parker Signer Name: Andrea Parker Signing Reason: I approve this document Signing Time: 24-Jan-2023 | 10:05:49 PST 67ACA71D7793463992E8671996F70B01 Signature Adoption: Pre-selected Style Signature ID: 67ACA71D-7793-4639-92E8-671996F70B01 Using IP Address: 174.119.205.244 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 24-Jan-2023 | 09:36 Viewed: 24-Jan-2023 | 10:05 Signed: 24-Jan-2023 | 10:05
Electronic Record and Signature Disclosure: Accepted: 24-Jan-2023 | 10:05 ID: a7957894-cfd2-4723-9adc-34fde4b6ee8f		
Andrew Hamer andrew.hamer@cardiolrx.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Signer Name: Andrew Hamer Signing Reason: I approve this document Signing Time: 24-Jan-2023 | 12:03:11 PST 4B9572D0C730410A90A26CB6E4EF4E75 Signature Adoption: Uploaded Signature Image Signature ID: 4B9572D0-C730-410A-90A2-6CB6E4EF4E75 Using IP Address: 50.207.75.92 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 24-Jan-2023 | 10:06 Viewed: 24-Jan-2023 | 12:02 Signed: 24-Jan-2023 | 12:03
Electronic Record and Signature Disclosure: Accepted: 24-Jan-2023 | 12:02 ID: 09c0c385-156c-4d0b-92b4-d52b49d9da8f		

Signer Events	Signature	Timestamp
Stuart Pocock Stuart.Pocock@lshtm.ac.uk Professor Security Level: Email, Account Authentication (Required)	DocuSigned by: Stuart Pocock Signer Name: Stuart Pocock Signing Reason: I approve this document Signing Time: 25-Jan-2023 | 02:58:02 PST F93DFA76DBAB416694E07C33050AFAED Signature Adoption: Pre-selected Style Signature ID: F93DFA76-DBAB-4166-94E0-7C33050AFAED Using IP Address: 194.80.229.244 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 24-Jan-2023 | 12:03 Viewed: 24-Jan-2023 | 12:17 Signed: 25-Jan-2023 | 02:58
Electronic Record and Signature Disclosure: Accepted: 24-Jan-2023 | 12:17 ID: 0d2aa538-6b72-4434-940c-21d66264ce5c		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
Robin White robin.white@worldwide.com Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 24-Jan-2023 | 09:36 Resent: 25-Jan-2023 | 02:58 Viewed: 24-Jan-2023 | 09:46

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	24-Jan-2023 | 09:36
Certified Delivered	Security Checked	24-Jan-2023 | 12:17
Signing Complete	Security Checked	25-Jan-2023 | 02:58
Completed	Security Checked	25-Jan-2023 | 02:58

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

From time to time, Worldwide Clinical Trials (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign, Inc. (DocuSign) electronic signing system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies
At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after signing. If you wish for us to send you paper copies of any such documents from our office to you, you should contact the originator of the document.

Withdrawing your consent
If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind
If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of a DocuSign envelope instead of signing it. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically
Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures

electronically from us.

How to contact Worldwide Clinical Trials
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows.

To advise Worldwide Clinical Trials of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to the originator of your document and in the body of such request you must state: your previous e-mail address and your new e-mail address.
In addition, you must notify DocuSign, Inc. to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in the DocuSign system.

To request paper copies from Worldwide Clinical Trials
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send an e-mail to the originator of the document and in the body of such request you must state your e-mail address, full name, postal address, and telephone number.

To withdraw your consent with Worldwide Clinical Trials
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

1. decline to sign a document from within your DocuSign session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
2. send an e-mail to the originator of your document and in the body of such request you must state your e-mail, full name, postal address, and telephone number.

Required hardware and software

Operating Systems	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution	800 x 600 minimum
Enabled Security Settings	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically
To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I agree' box, I confirm that:

- **I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC CONSUMER DISCLOSURES document; and**
- **I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and**
- **My electronic signature is the legally binding equivalent of my handwritten signature; and**
- **Until or unless I notify Worldwide Clinical Trials as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by Worldwide Clinical Trials during the course of my relationship with you.**

From time to time, Worldwide Clinical Trials (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign, Inc. (DocuSign) electronic signing system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to these terms and conditions, please confirm your agreement by clicking the 'I agree' button at the bottom of this document.

Getting paper copies
At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after signing. If you wish for us to send you paper copies of any such documents from our office to you, you should contact the originator of the document.

Withdrawing your consent
If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind
If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. To indicate to us that you are changing your mind, you must withdraw your consent using the DocuSign 'Withdraw Consent' form on the signing page of a DocuSign envelope instead of signing it. This will indicate to us that you have withdrawn your consent to receive required notices and disclosures electronically from us and you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically
Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures

electronically from us.

How to contact Worldwide Clinical Trials
You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows.

To advise Worldwide Clinical Trials of your new e-mail address
To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to the originator of your document and in the body of such request you must state: your previous e-mail address and your new e-mail address.
In addition, you must notify DocuSign, Inc. to arrange for your new email address to be reflected in your DocuSign account by following the process for changing e-mail in the DocuSign system.

To request paper copies from Worldwide Clinical Trials
To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send an e-mail to the originator of the document and in the body of such request you must state your e-mail address, full name, postal address, and telephone number.

To withdraw your consent with Worldwide Clinical Trials
To inform us that you no longer want to receive future notices and disclosures in electronic format you may:

1. decline to sign a document from within your DocuSign session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
2. send an e-mail to the originator of your document and in the body of such request you must state your e-mail, full name, postal address, and telephone number.

Required hardware and software

Operating Systems	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution	800 x 600 minimum
Enabled Security Settings	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically
To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.

By checking the 'I agree' box, I confirm that:

- **I can access and read this Electronic CONSENT TO ELECTRONIC RECEIPT OF ELECTRONIC CONSUMER DISCLOSURES document; and**
- **I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and**
- **My electronic signature is the legally binding equivalent of my handwritten signature; and**
- **Until or unless I notify Worldwide Clinical Trials as described above, I consent to receive from exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to me by Worldwide Clinical Trials during the course of my relationship with you.**