Clinical Investigation Plan

Safe and Timely Antithrombotic Removal – Direct Oral Anticoagulants Apixaban & Rivaroxaban (STAR-D): A Prospective, Multi-center, Double-blind, Randomized, Study to Evaluate DrugSorb™-ATR Removal of Apixaban and Rivaroxaban to Reduce Likelihood of Serious Bleeding in Patients Undergoing Urgent Cardiothoracic Surgery.

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Sponsor:
CytoSorbents, Inc.
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Victoria T. Lee, MD

SIGNATURE PAGE – SPONSOR APPROVAL

This Clinical Investigation Plan is in accordance with the clinical research guidelines established by the US Code of Federal Regulations (Title 21, Parts 50, 54, 56, and 812), the regulations and guidelines of International Council for Harmonisation for Good Clinical Practice, and International Organization for Standardization 14155 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice). Study documents will be maintained in accordance with applicable regulations.

SPONSOR APPROVAL

I have read the Clinical Investigation Plan and approve it:

09-March-2022

Victoria T. Lee, MD
Senior Director of Clinical Affairs

Date

BRIEF PROTOCOL REVISION HISTORY

Version	Date	Brief Description of Changes
1.0	09-September-2021	Original Submission
1.1	22-September-2021	The following sections and subsections were updated to address review suggestions by the Agency: • Synopsis • Section 4.4.1 Inclusion Criteria • Section 4.4.2 Exclusion Criteria • Section 10 Concomitant Medications • Appendix 4. Table 6. Schedule of Assessments The following sections were updated to rectify errors from the initial document • Section 4.4.2 Exclusion Criteria • Section 11.1 Statistical Power and Sample Size Determination • Appendix 5
1.2	28-September-2021	The following sections and subsections were updated to address review suggestions by the Agency: • Synopsis • Section 4.4.2 Exclusion Criteria • Section 11.3 Effectiveness Analysis Footnote "b" in Appendix 2 and footnote "f" in Table 6 updated to match exact language of exclusion criterion #10
1.3	13-October-2021	Typographic errors corrected in the following locations: • Document header, pages 71-73 • Duration of screening period in **Table 6**. Schedule of Assessments (two locations: 1) timepoint box and 2)

		footnote "e") **Section 9.2.1 Adverse Events** updated to include additional safety reports requested by the Agency at intervals independent of annual IDE safety reporting
2.0	25-February-2022	• Increased number of study sites from 25 to 30 • Language around inclusion criteria #3 has been updated to allow enrollment of patients with up to 36hrs of time between last apixaban or rivaroxaban dose and start of surgery. The change to the inclusion criteria itself is reflected in the protocol **Synopsis** and **Section 4.4.1** *Inclusion Criteria.* References to this time-point have been updated through-out the remainder of the text as relevant (including in **Table 5** and **Table 6** of the protocol appendices) • Language around exclusion criteria #1 has been revised to exclude those patients who have had >48hrs between last apixaban/rivaroxaban dose and start of surgery. This update has been made within the protocol **Synopsis** and **Section 4.4.2** *Exclusion Criteria* • Language has been added to exclusion criterion **#3** to clarify intent of excluding subjects whose index operation is for "*implant or revision of LVAD or RVAD.*". This update has been made in the **Synopsis** and Protocol **Section 4.4.2** (*Exclusion Criteria*) • Language has been added within exclusion criterion **#12** to clarify that the 30-day life expectancy does not include "*the critical condition that is requiring the cardiac operation under study*." This update has been made in the **Synopsis** and Protocol **Section 4.4.2** (*Exclusion Criteria*) • "Primary endpoint (Win Ratio) results stratified by DOAC (apixaban vs. rivaroxaban) type" has been removed as an "Additional Secondary Effectiveness Endpoint." This change was made to the protocol **Synopsis** and **Section 4.3.3** (*Additional Secondary Effectiveness Endpoints*) and **Section 11.3** (*Effectiveness Analysis*) • **Section 9.2.5** (Physical Exam) and footnote "r" in **Table 6** has been updated to allow physical exams performed as part of standard of care on the day of screening to be documented as a screening assessment • The following sections/subsections were updated to address Statistical Considerations proposed by the Agency in their response to the STAR-D IDE: **Section 11** (*Statistical Considerations*), **Section 11.1** (*Statistical Power and Sample Size Determination*), and **Section 11.3** • The definition of the modified intent-to-treat (mITT) population has been updated in the **Synopsis** and **Section 11.2** (*Analysis Populations*) • The definition of the Safety Analysis population has been updated in the Synopsis and **Section 11.2** (*Analysis Populations*) • The primary analyses of the trial will be performed on the modified intent-to-treat (mITT) population rather than the intent-to-treat (ITT) population. This language has been updated in the protocol **Synopsis** and **Section 11.2** *Analysis Populations* accordingly • New section added: **Section 11.4** *Subgroup Analysis*

		• The stopping boundaries for the pre-specified interim analysis have been updated in **Section 11.6** (*Interim Analysis*) at the guidance of the DSMB. Rather than the Lan-DeMets Pocock approximation, a Lan-DeMets O'Brien-Fleming spending function is instead being used for determination of stopping boundaries (which are now more conservative than prior) ○ Power calculations within **Table 3** (*Win Ratio Effect Size Assumptions and Power and Sample Size Estimates Under Varying Conditions*) have been updated to reflect changes related to the new stopping boundaries • **Appendix 2** has been updated to reflect the Schedule of Assessments (**Table 6**) more accurately by clearly distinguishing the timing of Point of Care Tests (*ACT*) as compared to the timing of local laboratory coagulation tests (*Coagulation Panel*). The updated language does not alter the timing of assessments as described in the protocol but reduces confusion from similar terminology
2.1	09-March-2022	• Additional language update to exclusion criterion #12, per FDA Interactive Review: "*Subjects with life expectancy of <30 days (not inclusive of the critical condition that is requiring the cardiac operation under study for which there is a reasonable expectation that cardiac surgery with the device may prolong life for more than 30 days*" • **Section 11.6** (*Interim Analysis*) has been further modified to include the following points: a) the Sponsor will defer to the DSMB for decision on early study termination at the time of the interim analysis, and b) the FDA will be immediately notified of the decision of whether the study has been halted or terminated

SIGNATURE PAGE – INVESTIGATOR AGREEMENT

This Clinical Investigation Plan is in accordance with the clinical research guidelines established by the US Code of Federal Regulations (Title 21, Parts 50, 54, 56, and 812), the regulations and guidelines of International Council for Harmonisation for Good Clinical Practice, and International Organization for Standardization 14155 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice). Study documents will be maintained in accordance with applicable regulations.

INVESTIGATOR AGREEMENT

I have read the Clinical Investigation Plan and agree to conduct the investigation as described herein.

_____
Principal Investigator (Printed)

_____ _____
Principal Investigator (Signature) Date

_____
Clinical Site

SYNOPSIS

Title of investigation: Safe and Timely Antithrombotic Removal – Direct Oral Anticoagulants Apixaban & Rivaroxaban (STAR-D): A Prospective, Multicenter, Double-blind, Randomized, Study to Evaluate DrugSorb™-ATR Removal of Apixaban and Rivaroxaban to Reduce Likelihood of Serious Bleeding in Patients Undergoing Urgent Cardiothoracic Surgery.

Objectives:

- To demonstrate reductions in surgical and early post-surgical bleeding with the intraoperative use of DrugSorb™-ATR in patients undergoing cardiothoracic surgery ≤36hrs since last apixaban or rivaroxaban dose.
- To demonstrate reductions in apixaban or rivaroxaban blood levels (Δ[DOAC]) with the intraoperative use of DrugSorb™-ATR.
- To establish the safety of the intraoperative use of DrugSorb™-ATR in the intended population.

Background and rationale:

Apixaban and rivaroxaban are both factor Xa inhibitors that fall into a category of drugs generally referred to as direct oral anticoagulants (DOACs). They share significant similarities, as both of these DOACs are indicated for stroke prevention in patients with non-valvular atrial fibrillation (A. fib), and for secondary prevention of venous thromboembolic events (VTE).[1] [2] Together, apixaban and rivaroxaban account for the vast majority of DOAC use in both the U.S and globally, with >75% of the U.S Medicare market share since 2015. [3] Data from the Medical Expenditure Panel Survey (MEPS), show that apixaban is prescribed more frequently than rivaroxaban resulting in an approximate 3:2 ratio in the year 2018 (*https://meps.ahrq.gov/mepstrends/hc_pmed/*), however market data suggests that apixaban has had further gains since that time.[4, 5] As with all antithrombotic medications, the predominant safety concern associated with DOAC use is bleeding, whether spontaneous or secondary to injury or invasive/surgical procedures. As such, DOAC therapy is routinely stopped for several days prior to invasive/surgical procedures in current clinical practice. The 2017 ACC Expert Consensus Decision Pathway and the 2018 European Heart Rhythm Association Practical Guide on use of non-vitamin K antagonist DOACs in patients with atrial fibrillation specifically recommend that both apixaban and rivaroxaban should be discontinued at least 48hrs prior to elective cardiothoracic surgeries (which are known to carry a high risk of major bleeding). [6] [7] It is widely accepted that longer periods of DOAC interruption may be necessary for patients with impaired renal function, or those on concomitant medications that may decrease the efficiency of drug metabolism (such as several antiarrhythmic agents).[8]

However, published reports suggest that ~10% of patients on chronic DOAC therapy will require urgent or emergent procedures annually. [9] In such situations, scheduled pre-operative drug discontinuation is generally not possible, thus exposing these patients to high bleeding risk. This is especially relevant in cases of urgent cardiothoracic surgery where the presence of antithrombotic agents greatly increases the risk of life-threatening bleeding. [10]

The DrugSorb™-Anti Thrombotic Removal (ATR) device has high affinity for binding hydrophobic small molecules and drugs (~5-kDa to 60-kDa). Data on the antithrombotic drug removal capabilities of DrugSorb™-ATR have previously been published in Europe under the name CytoSorb®, which has been CE marked for both ticagrelor and rivaroxaban removal. DrugSorb™-ATR is the name of the device in the U.S, specifically intended to align with intended use in antithrombotic drug removal (ATR). Within this clinical investigation plan, the name CytoSorb® will be used when citing previously published data, to remain consistent with the literature.

DrugSorb-ATR can efficiently remove apixaban and rivaroxaban from whole blood.
Benchtop experiments published by Koertge et. al. utilized a small *in vitro* recirculation model with human whole blood, in which 91.6% of circulating rivaroxaban was removed within 1hr of recirculation. [11] Sponsor preclinical studies have supported these results, demonstrating approximately 95.1% removal of rivaroxaban from bovine whole blood after one hour of DrugSorb-ATR hemoadsorption (data on file, CytoSorbents).

Preclinical studies with the same experimental setup have also been performed with apixaban and

demonstrated 96.3% removal from bovine whole blood following one hour of DrugSorb-ATR hemoadsorption (data on file, CytoSorbents). Indeed, the drug removal curves were nearly identical for both apixaban and rivaroxaban, with >60% of the circulating drug removed within the first 15 minutes of DrugSorb-ATR exposure.

A retrospective case-series from Asklepios Klinik St. Georg (Hamburg, Germany) evaluated the use of the CytoSorb® device in patients on rivaroxaban undergoing emergent cardiothoracic surgery with cardiopulmonary bypass (CPB). Patients on rivaroxaban operated on CPB alone (control) were compared to patients operated on CPB with CytoSorb® (treatment). Results showed significant reductions in multiple measures of postoperative bleeding for patients managed with CytoSorb® compared to the control cohort. [12] No device-related adverse events (AEs) or device malfunctions/deficiencies were reported. No similar series has yet been published for patients on apixaban, however a case report by Mendes et. al. was published in 2020, in which they used the CytoSorb® device to treat a high-risk elderly female undergoing emergent redo mitral valve replacement on apixaban.[13] The subject did well post-operation, and suffered no bleeding complications. Given the similar drug removal mechanics in benchtop models, and the consistent clinical experience to date, it is expected that DrugSorb-ATR will provide the same clinical benefits in patients who are on *either* apixaban *or* rivaroxaban.

Thus, the Sponsor proposes to conduct a prospective, multi-center, double-blind, randomized, clinical trial to demonstrate that use of DrugSorb-ATR during CPB significantly reduces surgical and early post-surgical bleeding and efficiently removes apixaban and rivaroxaban in patients undergoing cardiothoracic surgery within 36 hours of their last dose.

Hypothesis:
In patients undergoing cardiothoracic surgery on CPB within 36 hours of last apixaban or rivaroxaban dose, intraoperative use of DrugSorb-ATR will significantly reduce surgical and post-surgical bleeding complications.

Endpoints:
Primary Effectiveness Endpoint:

- Surgical and early post-surgical bleeding, assessed by the ranked composite of:
  1) Fatal bleeding occurring within 48hrs post-index operation,
  2) Moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and
  3) 24-hour chest tube drainage.

Key Secondary Effectiveness Endpoints:

- Change in blood apixaban levels (Δ[apixaban]) pre- vs. post-CPB measured by liquid chromatography/tandem mass spectrometry,
- Change in blood rivaroxaban levels (Δ[rivaroxaban]) pre- vs. post-CPB measured by liquid chromatography/tandem mass spectrometry.

Additional Secondary Effectiveness Endpoints:

- 24-hour chest tube drainage (volume);
- Total platelet transfusions during hospitalization (volume and units);
- Total PRBC transfusions during hospitalization (volume and units);
- Total UDPB events (by class);
- All surgical re-exploration for excessive bleeding
- Total fatal perioperative bleeding events

Exploratory Endpoints:

- Area under the concentration time curve (AUC), for intraoperative apixaban or rivaroxaban pharmacokinetic (PK) concentration
- Duration of index operation (minutes);
- Length of ICU stay;
- Length of hospital stay;
- 30-day hospital readmissions.

Primary Safety Endpoint:

- GCP-level assessment of all AEs during the study period

Additional Safety Endpoints:

- 30-day cardiac mortality
- 30-day all-cause mortality;
- Postoperative stroke during index hospitalization
- Postoperative myocardial infarction (MI) during index hospitalization
- Urgent postoperative coronary revascularization during the index hospitalization
- Postoperative venous thromboembolic events (VTE) during index hospitalization
- Serious device-related adverse events

Investigational design:
This study is a prospective, multi-center, double-blind, randomized pivotal trial to evaluate the safety and effectiveness of DrugSorb-ATR to reduce surgical and early post-surgical bleeding in patients undergoing cardiothoracic surgery requiring CPB ≤36hrs after last dose of apixaban or rivaroxaban. Bleeding will be measured by a ranked composite endpoint of: fatal bleeding occurring within 48hrs of the index operation, moderate, severe, or massive perioperative bleeding events (UDPB ≥2), and 24-hour chest tube drainage. Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) alone (control arm) or standard of care plus intraoperative apixaban/rivaroxaban removal with DrugSorb-ATR integration in the CPB circuit (investigational arm). In the control arm a sham device that is not actively connected to the CPB circuit will be placed in the identical location as the DrugSorb-ATR cartridge in the investigational arm, with the entire set-up covered by a drape to maintain the blind. Subjects will be followed out to 30 days after the surgical procedure for assessments of adverse events (AE) and survival.

Prior to randomization, subjects will be stratified based on a) DOAC type (either apixaban or rivaroxaban), b) site, and c) type of planned cardiothoracic surgery [either CABG alone, or all other surgeries (including but not limited to combination cardiac procedures, and aortic interventions)]. Stratification is intended to control for potential confounding effects arising from differing drug therapies, institutional practices, and from procedure-specific CPB duration (i.e., device exposure – treatment duration) and bleeding risk.

As apixaban and rivaroxaban have a similar mechanism of action, approved use indications, bleeding risk, and response to the investigational therapy, the trial will evaluate both drugs as a **combined population** for effectiveness and safety. The intent is to have a balanced contribution of apixaban and rivaroxaban patients in the trial with each drug contributing a target minimum of 40% of the total study population at the time of final analysis.

Number of subjects:
Approximately 120 subjects will be randomized into the study (60 into each arm). Assuming a 5% dropout rate, at total of 114 subjects (57 per arm) are expected to be evaluable for effectiveness and safety.

Number of sites:
Approximately 30 investigational sites in the US will participate in the study.

Subjects must meet all inclusion criteria to be eligible to participate in the study. Subjects meeting any of the exclusion criteria are not eligible to participate in the study.

Inclusion criteria:

1. Males and females aged ≥18
2. Written full informed consent
3. Cardiothoracic surgery requiring CPB ≤36 hours from the last dose of either apixaban or rivaroxaban:
    - CABG alone
    - Valve repair or replacement
    - Combination surgery (i.e., CABG + valve operation)

- Aortic surgery

Only patients taking apixaban or rivaroxaban for one of the following indications are eligible for enrollment: a) reduction of stroke/systemic embolism in nonvalvular atrial fibrillation, or b) initial or extended treatment of a venous thromboembolic event (VTE) which includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

Exclusion criteria:

1. Cardiothoracic surgery >48 hours after last known dose of apixaban or rivaroxaban
2. Patients on low dose apixaban or rivaroxaban for prophylactic indications (see **Section 4.4.2** for details)
3. Heart-lung transplant procedures
4. Procedures for ventricular assist device (i.e., implant or revision of LVAD or RVAD)
5. Any of the below conditions that pose a known risk for increased bleeding:
   - Heparin induced thrombocytopenia
   - Preoperative platelet count < 50,000 μ/L
   - Hemophilia
   - INR ≥ 1.8
6. Prohibited concomitant antithrombotic medications (reference Appendix 5 of study protocol);
7. Acute sickle cell crisis
8. Known allergy to any of the device components
9. Subjects with active (untreated) systemic infection
10. Subjects with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed
11. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are breast-feeding
12. Subjects with life expectancy of <30 days (not inclusive of the critical condition that is requiring the cardiac operation under study for which there is a reasonable expectation that cardiac surgery with the device may prolong life for more than 30 days)
13. Inability to comply with the requirements of the study protocol
14. Treatment with an investigational drug or device within 30 days prior to surgery
15. Subjects with previous enrollment in this trial

Duration of subject participation in the investigation:
Duration of treatment with the DrugSorb-ATR device is limited to the CPB duration. Subjects will undergo scheduled study procedures until hospital discharge. Hospital discharge means the date of initial discharge from the hospital after the index procedure, irrespective of whether the subject is discharged to home care, secondary care or other rehabilitation unit.

Study follow-up will continue out to 30-days after the index operation to monitor occurrence of adverse events and vital status of study participants.

Test device and subject treatment:
DrugSorb-ATR is a sorbent-filled hemoperfusion cartridge that can efficiently adsorb apixaban and rivaroxaban, and thereby reduce circulating drug levels in blood. The device is placed into a parallel bypass circuit (between the oxygenator and the venous reservoir) to the main blood flow in a standard CPB circuit. Standard CPB anticoagulation protocols will be followed since Heparin is not adsorbed by DrugSorb-ATR.

Statistical methods:

Effectiveness Analysis

The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components: a) fatal bleeding events occurring within 48hrs of the index procedure, b) moderate, severe, or massive bleeding based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and c) 24-hour chest tube drainage (volume, mL). The Win Ratio assigns "wins", "losses", or "ties" between randomized groups in a serial fashion across all components of the composite endpoint adhering to the declared hierarchical order from higher to lower clinical importance.[14] [15] A ratio of "wins" greater than 1.0 favors the treatment arm; when the lower bound of a 95% confidence interval (CI) around the ratio exceeds 1.0, the treatment is shown to be statistically superior to control at alpha = 0.05. The primary effectiveness analysis will be performed in the overall study population comprised of both apixaban and rivaroxaban patients to evaluate the difference between the SOC (control) arm and the DrugSorb-ATR (investigational) arm.

The key secondary effectiveness endpoints are the pre-CBP vs. post-CPB change in drug levels (apixaban and/or rivaroxaban) measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS) [drug removal endpoint]. Change in each subject's blood concentration of apixaban or rivaroxaban from immediately *before* to immediately *after* CPB will be collected and analyzed by a central core laboratory. Drug removal will be analyzed for apixaban and rivaroxaban independently.

Change from baseline in blood concentration of apixaban or rivaroxaban is defined as:

$$\frac{\text{pre-CPB } [\text{apixaban}]_{\text{blood}} - \text{post-CPB } [\text{apixaban}]_{\text{blood}}}{\text{pre-CPB } [\text{apixaban}]_{\text{blood}}} * 100\%$$

or

$$\frac{\text{pre-CPB } [\text{rivaroxaban}]_{\text{blood}} - \text{post-CPB } [\text{rivaroxaban}]_{\text{blood}}}{\text{pre-CPB } [\text{rivaroxaban}]_{\text{blood}}} * 100\%$$

Based on existing benchtop evidence, a conservative estimate of 40% reduction in blood concentration of DOAC between pre- and post- DrugSorb-ATR removal is expected, with a standard deviation of 40%, in the treatment arm. Minimal change is expected in the control arm. A two-sample t-test will be used to evaluate the difference between treatment arms.

Additional powered secondary endpoints include 24-hour CTD (volume [mL]), total platelet transfusions (volume [mL] and units), and total PRBC transfusions (volume [mL] and units) during the index hospitalization. Twenty-four-hour CTD (mL) will be assessed via two-sample t-test for mean difference. The transfusion endpoints will all be analyzed using two-sample t-tests for mean differences, and Fisher-Freeman-Halton exact tests for units. In the event the assumptions for a two-sample t-test are not met in any of the above, a nonparametric test such as a Mann-Whitney test will be employed, with median and range values provided in the output. An additional analysis of 24-hour CTD will compare the frequency of subjects falling into volume categories (i.e., <500 mL, 500 to <750 mL, 750 to <1000 mL, 1000 to <1250 mL, 1250 to <1500 mL, and ≥1500 mL), and will use a Fisher-Freeman-Halton exact test to compare treatment groups. Other secondary endpoints include the remaining Win Ratio component parts: proportions of fatal perioperative bleeding events will be assessed via Fisher's exact test; and proportions of UDPB events (by category) will be assessed via a Fisher-Freeman-Halton exact test. The secondary endpoint of surgical re-exploration for bleeding will take into account time to re-exploration.

Sample Size

Approximately 120 subjects will be randomized in a 1:1 ratio to the treatment and control arms. Assuming a 5% dropout rate, at total of 114 subjects (57 per arm) are expected to be evaluable for effectiveness and safety. Sample size is based on assumed response rates for the primary effectiveness endpoint, and power can be calculated via an iterative simulation process with programming code available in an appendix to Redfors et al. (2019).[16] With a Finkelstein-Schoenfeld test, total of 57 subjects per arm ensures power of >99.2%, using a two-sided alpha (α) of 0.05, and assuming an interim analysis for efficacy at 70% completion. Power for each of the key secondary endpoints is estimated at 96.3%, and for 24-hour chest tube drainage (mL), >99.9%, based on a two-sample t-test assuming equal variance and a two-sided alpha of 0.05.

Similarly, although assuming unequal variances, power for comparisons of platelet transfusions (volume [mL]) and PRBC transfusions (volume [mL]), is estimated at 98.0% and 96.7%, respectively.

Interim Analysis
A planned interim analysis will be performed after 70% of study subjects have completed the study, to allow for early stopping for overwhelming efficacy according to a pre-specified boundary.

Subgroup Analyses
Subgroup analyses will be conducted to investigate efficacy of treatment. These include analyses by DOAC drug type, site, and type of planned cardiothoracic surgery.

Analysis Populations
Enrolled subjects include all subjects who provide informed assent/consent. Enrolled subjects who do not meet criteria for study eligibility are screening failures and will exit the study.

The Intent-to-Treat (ITT) Population will include all enrolled (assented/consented) subjects who are randomized. The modified Intent-to-Treat (mITT) Population will include all randomized subjects who undergo the index surgical procedure **and** receive a study device (whether DrugSorb-ATR or *sham*). The primary analyses of the trial will be performed on the mITT Population. Baseline demographic and clinical variables will be summarized for each of the treatment groups for the ITT and mITT populations. So long as the ITT and mITT populations are not identical, the ITT patients who do not fall within the mITT population will be presented in a listing, including the reasons for why they did not receive a study device The Per Protocol (PP) Population will include all mITT subjects who have no major protocol violations. Analysis of the primary efficacy endpoint will be performed in the PP population as a sensitivity analysis.

The Safety Analysis Population will include all enrolled subjects who are treated or attempted treatment with a study device. "Attempted treatment" refers to any subject(s) who initiate treatment with a study device (whether DrugSorb-ATR or *sham*) during the index procedure but experience early discontinuation.

Safety Analysis
All AEs occurring after the start of the CPB procedure will be listed and summarized using descriptive methodology. The incidence of AEs will be presented by severity and by relationship to the investigational device (DrugSorb-ATR or sham) as determined by the Investigator (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities®. Observed values for clinical laboratory test data and vital signs, along with change from baseline results, will be summarized by collection time point. A summary of clinically notable values will be provided.

Safety oversight committees:
DSMB:
Three physicians with relevant clinical/medical and investigational expertise together with an independent statistician will form the Data Safety Monitoring Board (DSMB) that will be independently managed by an academic research organization. The primary role of the DSMB is to oversee the safety of subjects enrolled in the study and also oversee the interim analysis. All DSMB members will be independent from the investigative sites and the study sponsor. The schedule and process associated with DSMB activities will be outlined in the DSMB charter.

CEC:
An independent group of physicians with relevant clinical expertise relating to the study outcomes who are not otherwise involved in the study will act as the Clinical Events Committee (CEC). The CEC will be independently managed by an academic research organization. The CEC will be responsible for the review and adjudication of effectiveness endpoints and safety events that occur during study duration (i.e., within 30 days post-operation) according to standardized definitions as outlined in the CEC charter.

STUDY ORGANIZATION

Sponsor:
CytoSorbents, Inc.

Executive Committee:
Principal Investigators:
- **Michael Mack, MD (Baylor Scott & White Health)**
- **C. Michael Gibson, MD (Beth Israel Deaconess Medical Center)**

Members:
- **David J. Schneider, MD (University of Vermont Medical Center)**
- **E. Magnus Ohman, MD (Duke Health)**
- **Frank W. Sellke, MD (Brown University; Rhode Island Hospital and The Miriam Hospital)**
- **Vinod H. Thourani, MD (Piedmont Heart Institute)**
- **James D. Douketis, MD (St. Joseph's Healthcare Hamilton)**
- **Efthymios N. Deliargyris, MD (CMO, CytoSorbents Inc. Sponsor Representative)**

Clinical Events Committee (CEC):
Baim Institute for Clinical Research (previously known as the Harvard Clinical Research Institute)

Data Safety and Monitoring Board (DSMB):
Center for Interventional Cardiovascular Research and Clinical Trials, Icahn School of Medicine at Mount Sinai

Independent Statistician for the DSMB:
Stuart J. Pocock, PhD (London School of Hygiene & Tropical Medicine)

Contracted Research Organization (CRO):
Medpace

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	Acute coronary syndrome
ADE	Adverse device effect
ADP	Adenosine diphosphate
AE	Adverse event
A. FIB	Atrial fibrillation
ATR	Anti-Thrombotic Removal
AUC	Area under the concentration time curve
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPB	Cardiopulmonary bypass
CIP	Clinical investigation plan
CRO	Contract Research Organization
Cryoppt	Cryoprecipitate
DOAC	Direct Oral Anticoagulant
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
eCRF	Electronic case report form
EC	Ethics committee
ECG	Electrocardiogram
FDA	US Food and Drug Administration
FCS	Field Clinical Specialist
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IFU	Instructions for use
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IxRS	Interactive Voice/Web response
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NSTEMI	Non-ST segment elevation myocardial infarction
PAD	Peripheral Arterial Disease
PCC	Prothrombin complex concentrates
PE	Pulmonary Embolism
PK	Pharmacokinetic

PLT	Platelet concentrates
PP	Per Protocol
PRBC	Packed red blood cells
RCT	Randomized controlled trial
rFVIIa	Recombinant activated factor VII
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
UADE	Unanticipated adverse device effect
UDPB	Universal definition of perioperative bleeding in cardiac surgery
VTE	Venous thromboembolic event
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and Clinical Need

The risk of bleeding during cardiothoracic surgery is significantly increased by the presence of antithrombotic drugs, including direct oral anticoagulants (DOACs). [10] [17] Apixaban and rivaroxaban are factor Xa inhibitors that are both indicated for reduction in risk of stroke and systemic embolization in patients with non-valvular atrial fibrillation (A. fib), treatment of venous thromboembolism (VTE), and as prophylaxis of deep venous thrombosis.[1] [2] They are the two dominant representatives of the DOAC class in the US and worldwide.[18] Within the US Medicare population, apixaban and rivaroxaban in combination have accounted for >75% of the U.S DOAC market share since 2015. [3] By the first quarter of 2017, only 21.1% of commercial or Medicare Advantage patients on chronic oral anticoagulation for atrial fibrillation were being prescribed warfarin. In contrast, 50.1% were being prescribed apixaban, 25.0% rivaroxaban, and 3.8% dabigatran. [19] Consistent with Medicare data, the Medical Expenditure Panel Survey (MEPS) also demonstrated a market dominance of apixaban over rivaroxaban, with a prescription ratio of approximately 3:2 between the two drugs in the year 2018, and minimal usage of all the other DOACs (*https://meps.ahrq.gov/mepstrends/hc_pmed/*).

As with any anticoagulant, the predominant safety concern with DOAC use is the possibility of major bleeding events, especially in relation to surgery and thus drug discontinuation is recommended prior to surgery to reduce the risk of bleeding. [20] The 2017 ACC Expert Consensus Decision Pathway and the 2018 European Heart Rhythm Association Practical Guide on use of non-vitamin K antagonist oral anticoagulants recommend discontinuing apixaban and rivaroxaban at least 48hrs prior to surgeries carrying a high risk of major bleeding, including cardiothoracic surgery. [6] [7] It is widely accepted that longer periods of DOAC interruption may be necessary for patients with impaired renal function, or those on concomitant medications that may decrease the efficiency of drug metabolism (such as several antiarrhythmic agents). [8]

However, emergent, and urgent interventions are commonly required in cardiovascular patients, where there is no option for delay to allow full drug washout. According to a publication utilizing data from the Society of Thoracic Surgery (STS) Database from a major US medical center, >30% of CABG procedures in their experience were performed urgently, while an additional 3.6% of procedures were true emergencies. [21] As mentioned above, patients on DOACs undergoing cardiothoracic surgery without adequate time for natural washout experience very high rates of bleeding complications. [17] [10] Postoperative bleeding worsens overall prognosis, and in a study evaluating outcomes from urgent aortic surgeries, preoperative DOAC use was the leading risk factor associated with postoperative mortality. [17] The hazard ratio was 9.6, which was nearly 40% greater than the next-highest risk factor: extracardiac arteriopathy, and nearly 4x greater than the hazard ratio associated with recent MI (HR 2.5). [17] Incidence of re-operation for bleeding was 60% in the same population. This is a massive, 10-fold increase compared with a re-thoracotomy rate of only 6% in a population of patients with 4 days of DOAC washout prior to CT surgery. [22] In a study published by Hassan et al., it was demonstrated that timing of preoperative DOAC discontinuation strongly influenced post-operative 24hr chest tube drainage volume. [10] This metric has been demonstrated in the literature to strongly correlate with other critical outcomes including in-hospital mortality, increased need for postoperative supportive ventilation, and/or renal replacement therapy, transfusion volume, length of ICU stay, and length of hospital stay. [23] [24]

Thus, a real and significant unmet clinical need exists for an intervention to address the very high risk of bleeding, morbidity, and mortality among patients on DOACs who require urgent cardiothoracic surgery. Currently there are no U.S. approved alternatives to meet this significant unmet medical need. Apixaban and rivaroxaban together account for the vast majority of DOAC use, and currently management of urgent surgical patients on these two DOACs center on reversal of coagulopathy in

the setting of active bleeding. [3] [19] Historically, this included off-label use of non-specific pro-hemostatic agents such as prothrombin complex concentrate/activated prothrombin complex concentrate (PCC/aPCC) and KCentra® (4F-PCC), however supporting clinical evidence remains limited or controversial. [25] [26] More recently, Andexanet Alfa, a variant of human recombinant factor Xa received FDA approval (in 2018) for specific reversal of the oral factor Xa inhibitors in the setting of **life-threatening or uncontrolled bleeding**. [27] However, its safety and effectiveness has not yet been adequately tested in the surgical population. [28] It is for this reason, DrugSorb™-ATR has been designated a Breakthrough Device by the FDA for the removal of apixaban and rivaroxaban to reduce likelihood of serious bleeding in patients undergoing urgent cardiothoracic surgery.

1.2. Preclinical Data Informing Study Design

Preclinical studies have shown that both apixaban and rivaroxaban are rapidly and efficiently removed from whole blood by DrugSorb™-ATR hemoadsorption. Of note, DrugSorb™-ATR utilizes the same technology as the CytoSorb® device, which has previously received CE Mark approval for rivaroxaban removal in emergency CT surgery. To maintain consistent nomenclature with any referenced corresponding literature, DrugSorb™-ATR will be referred to by its historic name CytoSorb®, whenever published clinical and pre-clinical data on apixaban or rivaroxaban removal is cited.

Human Whole Blood Experiments

Experimental removal of **rivaroxaban** from human whole blood *ex vivo* by CytoSorb® hemoadsorption was performed utilizing a model device and 1,000 mL of citrate-anticoagulated blood with baseline rivaroxaban concentrations of 571 ± 20µg/L. [11] The model included a 60mL column containing the adsorbent beads typically found within the CytoSorb®-300mL device, and the blood was recirculated at a flow rate of 40mL/min for a total of 120min treatment time using a standard infusion pump. This relatively high drug concentration was selected to be well above the median therapeutic peak plasma concentrations seen in clinical use (which range from 46-270µg/L, depending on the indication for rivaroxaban therapy). Blood pH was monitored and adjusted to range from 7.35 to 7.45 by administration of Tris buffer, and blood temperature was maintained at 37°C. Blood was tested following 5min, 15min, 30min, 60min, and 120min of recirculation. Rivaroxaban concentrations were determined using chromogenic anti-factor Xa assays and drug-specific calibration (BIOPHEN Heparin LRT; HYPHEN BioMed, France). Within one hour of recirculation, 91.6% of circulating rivaroxaban was removed from the human whole blood. Between 60-120min of CytoSorb® hemoperfusion, the incremental decrease in rivaroxaban concentration was minimal. A similar recirculation system was studied without the CytoSorb® column, and after 5hrs showed no significant depletion of drug (data on file, CytoSorbents Corporation).

No human whole blood experiments have been performed for apixaban.

Bovine Whole Blood Experiments

Studies were conducted to evaluate the removal of **rivaroxaban** from bovine whole blood *ex vivo* by DrugSorb-ATR and were similar in design to the human whole blood experiments described above. [unpublished data] Approximately 4L of bovine whole blood spiked with 600ng/mL of rivaroxaban was recirculated within the model. Starting concentration of rivaroxaban was measured to be 450 ± 46ng/mL, a concentration exceeding standard therapeutic plasma drug levels (which range from 159.6-359.8ng/mL, depending on indication for treatment, and dosing schedule). [29] The control circuit was an identical system that incorporated an inactive device. The pump circulated blood through the DrugSorb-ATR cartridge at a rate of 300mL/min, which is similar to the rate used in humans. Blood samples to assay for rivaroxaban concentration were drawn from the reservoir bag at specific intervals after start of flow through the DrugSorb-ATR cartridge. Concentrations of

rivaroxaban were determined using tandem liquid chromatography mass spectrometry (LC-MS/MS). The results (**Figure 1**) showed that >95% of the rivaroxaban was removed from bovine whole blood *ex vivo* within 60 minutes of DrugSorb-ATR hemoadsorption (data on file, CytoSorbents Corporation).

Results from corresponding benchtop models for **apixaban** removal using DrugSorb-ATR are shown in **Figure 2** and demonstrate a nearly identical pattern of adsorption. As discussed above, the model incorporated a single DrugSorb-ATR cartridge into an extracorporeal circuit, using 4L of bovine whole blood. The blood was spiked with 300ng/ML of apixaban, resulting in a starting circulating concentration of 206.8 ± 8.1ng/mL. Again, this is in excess of standard therapeutic plasma drug levels. [30] Results demonstrated that >95% of the apixaban was removed from the bovine whole blood *ex vivo* within 60 minutes of DrugSorb-ATR hemoadsorption (data on file, CytoSorbents Corporation).

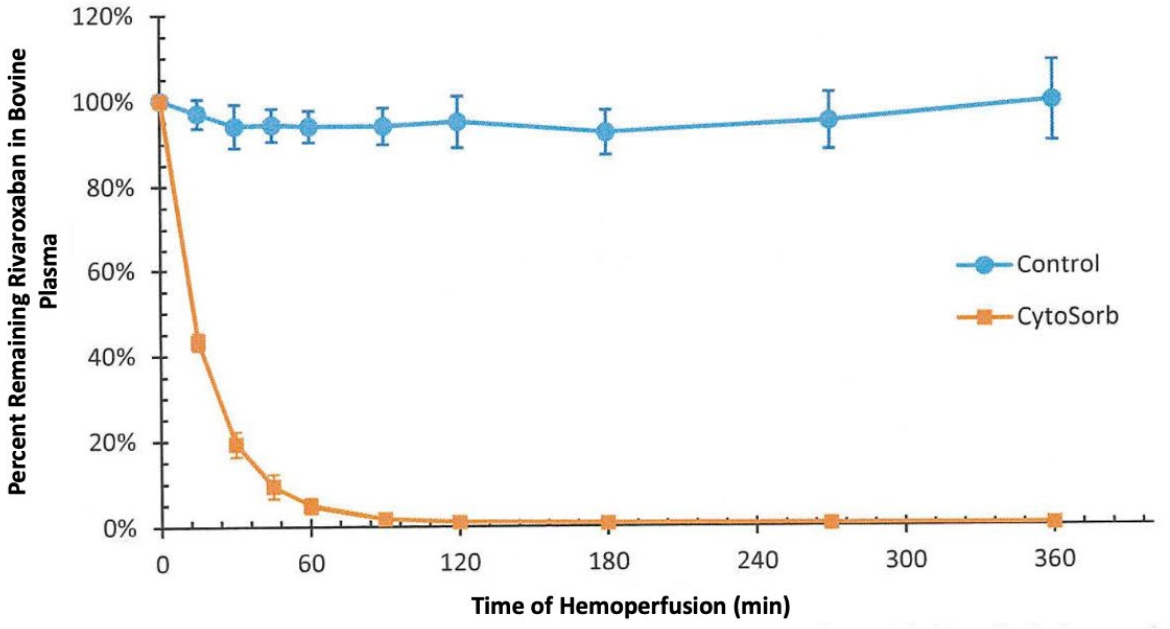


Figure 1. Removal of Rivaroxaban From Whole Bovine Blood *Ex Vivo*

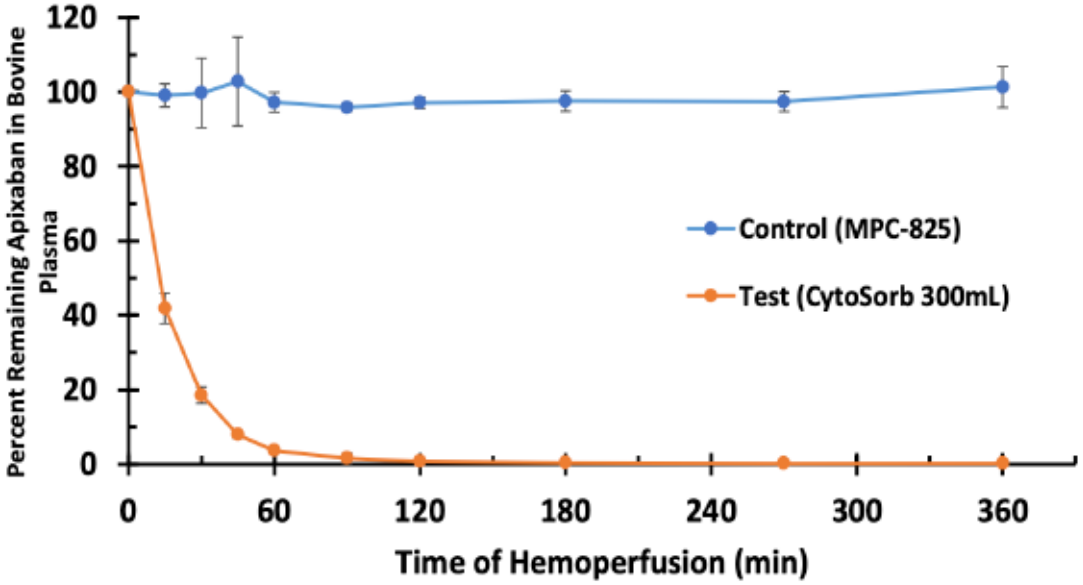


Figure 2. Removal of Apixaban From Whole Bovine Blood *Ex Vivo*

1.3. Clinical Data Informing Study Design

To date, over 120,000 CytoSorb® treatments have been performed globally. It is estimated that approximately 10% of the treatments have been intra-operative on cardiopulmonary bypass (CPB) including a significant number for antithrombotic removal (ticagrelor and rivaroxaban, for which the device has CE mark approval). Overall, the device has a favorable safety profile without any unanticipated device related adverse events reported to date.

A retrospective case-control series from Asklepios Klinik St. Georg (Hamburg, Germany) evaluated the use of the CytoSorb® device in patients on **rivaroxaban** undergoing emergent cardiothoracic surgery with CPB. A historical cohort of patients who underwent standard surgery on CPB but without the use of CytoSorb® was compared to the cohort of patients who received CytoSorb® hemoadsorption during CPB. Results showed significant reductions in multiple measures of postoperative bleeding with the intra-operative use of CytoSorb® that included blood products transfused, 24-hr chest tube drainage volume, rate of surgical re-exploration, length of ICU and total hospital stay. [12] Importantly, no device-related adverse events (AEs), unanticipated adverse device events (UADEs) or device malfunctions were reported.

A case report published in 2020 described the use of the CytoSorb® device in an 83-year-old female on **apixaban** undergoing emergent redo mitral valve replacement at Laussanee University Hospital in Switzerland. [13] The patient's last dose of apixaban was 7 hours prior to surgery, and total CPB duration was 100 minutes. Apixaban-specific anti-factor Xa levels were monitored pre-and post-treatment. At the time of CPB initiation, the anti-factor Xa level was 114 ng/mL and dropped to 32 ng/mL after weaning off CPB. The patient suffered no postoperative bleeding complications or device-related adverse events.

1.4. Device Background and Nomenclature

DrugSorb™-ATR utilizes the same technology as the CytoSorb® device discussed in the above preclinical and clinical data. The name DrugSorb™-ATR was recently implemented to better align with intended use. As such, for the purposes of this study, the device will hereafter be referred to as

DrugSorb™-ATR whenever reference is being made to its use in the indication of antithrombotic drug removal.

1.5. Study Design

The STAR-D study is designed to demonstrate reductions in surgical and early post-surgical bleeding with the intraoperative use of DrugSorb-ATR in patients undergoing cardiothoracic surgery ≤36hrs after last apixaban or rivaroxaban dose. These patients have been demonstrated in the literature to be at risk for significant bleeding complications (as previously discussed in **Section 1.1**). The study also aims to establish the safety of intraoperative DrugSorb-ATR use in the target population.

The mechanism of action, approved indications for use, and expert guideline recommendations for perioperative management of apixaban and rivaroxaban (with a recommended washout of at least 48 hours) are effectively the same. [1, 2, 6] Accordingly, it is assumed within our study that subjects using either one of these DOACs will have the same bleeding risk and experience the same treatment effect from DrugSorb-ATR. Indeed, a real-world registry of perioperative DOAC management found no differences in the bleeding risk associated with either apixaban or rivaroxaban [31] and a pharmacokinetic study by Kruetz et. al. demonstrated similar plasma drug concentrations of both drugs beginning at ~24hrs after last dose. [32] Given the anticipated equivalency in our study for both drug removal and clinical outcomes between the apixaban and rivaroxaban subjects, they will be evaluated as a combined population when assessing treatment effect for the DrugSorb-ATR (investigational) arm as compared to SOC (control) arm. Drug removal, as assessed by serial intraoperative serum level measurements, will be evaluated individually for apixaban and rivaroxaban. DOAC drugs other than apixaban or rivaroxaban will not be specifically addressed or studied here, due to the infrequency of their use in the U.S population.

The mechanism of action for the investigational device is removal of apixaban and/or rivaroxaban from active circulation through hemoadsorption while the patient is on cardiopulmonary bypass. Thus, change in total blood concentration of apixaban and rivaroxaban following CPB will be measured as key secondary endpoints. To do so, patient blood samples will be obtained during the pre-operative, operative, and immediate post-CPB time periods for drug concentration testing. Sampling every 30 ± 15min for quantification of serial changes in blood DOAC levels will be performed through the first 2 hours of therapy on CPB. The subsequent drug removal curve will be analyzed as an exploratory endpoint for each drug. Additional outcome measures to be evaluated include those that are documented as part of routine care and are detailed in **Section 4.3**.

A planned interim analysis will allow for early stopping for overwhelming efficacy according to pre-specified boundaries. Details are provided in **Section 11.4**.

2. DRUGSORB™-ATR DESCRIPTION AND INTENDED USE

2.1. Description of the DrugSorb™-ATR Device and Principle of Operation

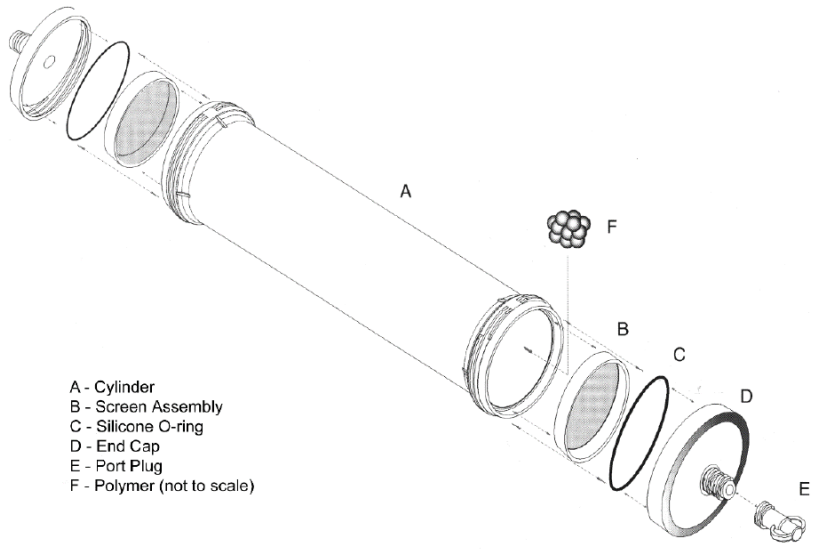
(*Note: This information is identical to the information provided in approved IDE G210081, and Breakthrough Device Designations Q200526 and Q211323.*)

DrugSorb-ATR is a sorbent-filled hemoperfusion cartridge (**Figure 3**). The cartridge consists of a cylinder and end-cap assembly filled with biocompatible porous polymer beads. At either end of the cylinder, a fine mesh screen is placed to retain the polymer beads within the device. Each endcap has a standard blood tubing connector, which is compatible with standard CPB blood tubing lines.

The polymer beads are composed of a divinylbenzene/polyvinyl pyrrolidone co-polymer, where each bead has hundreds of thousands of tightly controlled pores and channels that are generated via

suspension polymerization. These pores and channels, in turn, enable the porous polymer beads to remove middle molecular weight substances between ~5-kDa - 60-kDa, based on pore capture (size) and surface adsorption.

Figure 3. DrugSorb™-ATR



The polymer in the DrugSorb-ATR hemoadsorption cartridge is effective at binding small molecules with the molecular moieties contained in apixaban and rivaroxaban. These molecules easily pass into the pores of the polymer where it adsorbs onto the internal polymer surface. This surface adsorption is governed by the hydrophobic nature of the polymer, through a combination of non-polar interactions, hydrogen bonding, and Van der Waals forces. These drug-polymer interactions favor removal of hydrophobic molecules over hydrophilic ones.

DrugSorb-ATR is designed for use in extracorporeal circuits. For this investigation, the DrugSorb-ATR hemoadsorption cartridge will be incorporated as a shunt in the standard CPB circuit (**Figure 4**), in accordance with the device Instructions For Use (IFU). In standard subjects, flow rates through the DrugSorb-ATR cartridge should be maintained at 500 ± 100mL/min. In subjects on hypothermic circulatory arrest (HCA) where CPB flow rates are diminished, flow through the device should be maintained ≥100mL/min. In accordance with the IFU, maximum blood flow through the DrugSorb-ATR device should not exceed 700mL/min at any point during the procedure. Blood flow is controlled via an adjustable roller clamp distal to the cartridge and is monitored through ultrasonic flow detection (provided by Sponsor) to maintain a target blood flow consistent with protocol recommendations.

For this investigation the duration of device exposure will be limited to the duration of CPB since the use of DrugSorb-ATR will be initiated at the start of CPB and terminated at the end of CPB. Treatment is continuous and is expected to be of a shorter duration than the maximum treatment time provided in the IFU. Exceptions to continuous treatment could occur in the event of a device quality complaint (i.e., device deficiency/observation) in which case the treatment (and therefore the flow through the device) may be terminated before the end of CPB.

The intraoperative use of anticoagulants (e.g., heparin) in this investigation will be per the standard procedures of each clinical institution and in accordance with the IFU.

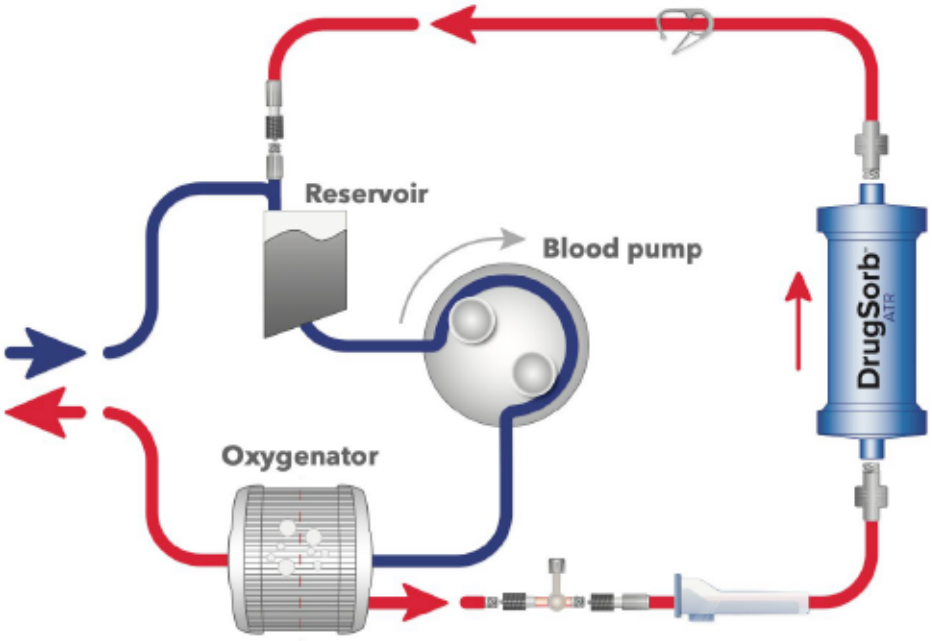


Figure 4. DrugSorb™-ATR Integration in the Cardiopulmonary Bypass Circuit

2.2. Treatment Materials

In addition to the DrugSorb-ATR hemoadsorption cartridge, the following components will be provided by the Sponsor:

- Disposable connector and tubing sets to connect the investigational device to the CPB circuit
- Standard roller clamp
- Disposable hemostats
- IFU of the device
- Training from a Field Clinical Specialist (FCS) to provide guidance on incorporating and using the device within a CPB circuit
- A Transonic® (or equivalent) flow detector

2.3. Device Accountability

The procedures for the accountability of investigational devices should follow the specifications below:

- Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigation Plan (CIP).
- The Sponsor or its designees shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites, use of the investigational devices, and either return or disposal.
- The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational devices, which shall include:
    - the date of receipt
    - identification of each investigational device (lot number and serial number)
    - the expiry date, if applicable
    - the date or dates of use

- patient identification
- the date of return of unused, expired, or malfunctioning investigational devices, if applicable

2.4. Use of the Investigational Device

The proposed investigative use of DrugSorb-ATR is for the removal of the DOACs apixaban and rivaroxaban, as an adjunct to the standard of care in subjects undergoing cardiothoracic surgery requiring CPB within 36 hours of receiving these medications. DrugSorb-ATR will only be used for this purpose as specified by this clinical protocol.

2.5. Investigational Device/Procedures Training

DrugSorb-ATR is easily integrated in a standard CPB circuit. In this study, one DrugSorb-ATR cartridge will be placed in a bypass circuit connected between the oxygenator and cardiotomy reservoir as shown in **Figure 4**, and separate from the main blood flow to the subject. Blood flow through this circuit is controlled via an adjustable roller clamp distal to the cartridges and monitored via ultrasonic flow detection to maintain flow.

The target flow rate through the device is to be 500 ± 100 mL/minute (approximately 15% to 20% of a typical flow rate in CPB). In patients on hypothermic circulatory arrest (HCA) where the clinical needs during CPB do not always allow the flow rate through the device to be maintained at 500 ± 100 mL/min, the flow rate through the device may range from 100 to 700 mL/min in accordance with the minimum/maximum parameters stated in the device IFU.

The circuit containing the DrugSorb-ATR cartridge will be connected prior to the start of the procedure. Blood flow through the DrugSorb-ATR cartridge will commence when the subject goes on CPB. Use of DrugSorb-ATR will stop at the end of CPB. At this time the entire circuit containing the device is flushed with saline or drained by gravity, which is consistent practice with all CPB circuits. The blood in the circuit is delivered back to the subject, per the hospital protocol.

DrugSorb-ATR training for the device users involved in this study will occur prior to any DrugSorb-ATR use and will be documented in a training log.

3. STUDY JUSTIFICATION

As discussed previously, apixaban and rivaroxaban have the same mechanism of action, the same indications for use, and are the most widely utilized DOACs in the U.S market. [1] [2] [19] As with any anticoagulant, patients undergoing surgical intervention in the setting of DOAC use carries a risk of bleeding. [33] Currently, there are no approved agents to either prevent or treat bleeding related to DOAC-induced coagulopathy in the surgical setting. Existing strategies for management of surgical patients on apixaban and rivaroxaban have prioritized preoperative drug washout wherever possible and use of non-specific pro-hemostatic agents with supportive strategies (blood product transfusions) when bleeding cannot be avoided. [25]

While recommendations for perioperative anticoagulant management in patients on Warfarin is supported by significant clinical experience, and determinants of perioperative outcomes in these patients are well-described in the literature, similarly robust data is lacking for the DOACs. [20] In the published literature, recommendations for perioperative management of patients on DOACs are based on drug half-life, renal function, and presumed bleeding risk of the planned procedure. [22] As discussed above, standard recommendations for DOAC washout prior to elective, high bleeding risk surgeries is ≥48hrs, but prolonged washout is recommended for patients with significantly impaired renal function. [6] [34] However, patients with emergent or urgent cardiovascular conditions

(including but not limited to acute ascending aortic dissection, left main or multi-vessel coronary disease not amenable to PCI, or complications of PCI) cannot always wait for this washout period, and may require surgery to avoid risking permanent injury, disability, or death.

Integration of a DrugSorb-ATR cartridge into the CPB circuit provides an option for clinicians to accelerate wash-out via active drug removal. In the previously discussed case report by Mendes et. al., when the authors extrapolated expected apixaban concentration based on half-life, they found that post- CytoSorb®+CPB levels of anti-factor Xa were 39-44% lower than would be anticipated from normal washout over the same period (range reflects expectations for normal vs. reduced renal function). [13] It is hypothesized that this accelerated removal of circulating DOAC will translate to significant reductions in surgical and post-surgical bleeding. This effect is most meaningful in those patients undergoing cardiac surgery ≤36 hours after their last DOAC dose, as these patients are *at greatest risk* of major bleeding complications due to *high residual drug* levels. Pre-clinical data demonstrate nearly identical drug removal rates for apixaban and rivaroxaban with DrugSorb-ATR. Based on the same mechanism of action, similar bleeding risks, and benchtop data suggesting consistent removal efficiency for both drugs, clinical treatment effect is also anticipated to be nearly identical. Accordingly, the trial will evaluate both drugs as a combined population for the primary effectiveness endpoint. The evaluable study population is planned to be similarly distributed with respect to apixaban and rivaroxaban, and monitoring will be employed throughout the study to ensure that each drug will contribute at least 40% of the study population at the time of final analysis.

Primary Effectiveness Endpoint: The composite primary endpoint of the trial was specifically constructed to assess the ability of DrugSorb-ATR to impact the full spectrum of surgical and early post-surgical bleeding. The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components ranked according to clinical importance. [14] [15] The three components are: a) fatal bleeding occurring within 48hrs post-index operation, b) moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and c) 24-hour chest tube drainage (mL).

The fatal bleeding events within the primary effectiveness endpoint are limited to the 48-hour postoperative window to include only those events likely to be modifiable by the intervention. Timing of re-initiation for therapeutic anticoagulation will be at the discretion of the treating physician, based on his/her assessment of continued bleeding risk vs. thrombotic risk (**Section 9.1.3**). Given that there is reasonable likelihood for resumption of anticoagulation as early as postoperative day two, there is high probability that fatal bleeding occurring >48 hours post-op would be independent of DrugSorb-ATR effectiveness.

The UDPB scale is a standardized bleeding definition that was specifically designed by experts to capture early bleeding after cardiac surgery and is based on the following 9 criteria occurring either in surgery or during the first postoperative day: (1) delayed sternal closure, (2) postoperative chest tube output, (3) packed red blood cell transfusion, (4) fresh frozen plasma transfusion, (5) platelet transfusion, (6) cryoprecipitate transfusion, (7) use of factor concentrates, (8) use of recombinant activated factor VII (rFVIIa), and (9) surgical re-exploration. [35] The UDPB scale defines 5 perioperative bleeding classes (0-4) as shown in **Table 1** (below). Importantly, it has been demonstrated that higher classification within the UDPB is associated with significantly worse immediate and late outcomes, including both in-hospital and 30-day mortality rates. [35] [36]

Table 1. Bleeding Class According to the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery

Class	Sternal closure delayed	Postoperative chest tube blood loss within 12 h (mL)	PRBC (units)	FFP (units)	PLT (units)	Cryoppt	PCCs	rFVIIa	Reexploration/ tamponade
0 (Insignificant)	No	< 600	0*	0	0	No	No	No	No
1 (Mild)	No	601-800	1	0	0	No	No	No	No
2 (Moderate)	No	801-1000	2-4	2-4	Yes	Yes	Yes	No	No
3 (Severe)	Yes	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes
4 (Massive)	N/A	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

PRBC = packed red blood cells; FFP = fresh frozen plasma; PLT = platelet concentrates; Cryoppt = Cryoprecipitate; PCCs = prothrombin complex concentrates; rFVIIa = recombinant activated factor VIIa; N/A, not applicable
For purposes of UDPB, PRBC, PLT, FFP, and Cryoppt transfusions are counted beginning **at chest closure**. PCC and rFVIIa transfusions are counted beginning at the start of the procedure.
* Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding. Prophylactic/preoperative transfusion of blood products and factor concentrates do not contribute to UDPB.

Exact measurement of postoperative blood loss is difficult, given that laboratory values such as hemoglobin and hematocrit are heavily influenced by intra- and postoperative fluid shifts, and transfusion protocols may vary by institution. However, chest tube drainage (CTD) in the early postoperative period (≤24 hours) is a metric that is easily quantifiable and routinely used in clinical practice. Enhanced Recovery After Surgery (ERAS) guidelines in cardiac surgery recommend chest tube placement and drainage to prevent accumulation of blood in the chest and mediastinum during the postoperative period, and their placement is standard of care following open cardiac surgery. [37]

The inclusion of CTD in the composite primary effectiveness endpoint is underscored by its clinical relevance evidenced by the use of CTD in everyday clinical practice protocols for postoperative decision-making (e.g., criteria for surgical re-exploration) that rely on rate and volume of chest tube drainage. [38] While postoperative CTD volume during the first 12 hours is already included within the UDPB classification, volume of 24-hr CTD has been identified as an important independent metric. The 24-hr CTD volume has been demonstrated to correlate with other important clinical outcomes, including transfusion requirements and duration of hospital stay in linear regression models. [39, 40] Excessive 24-hr CTD as defined by >1000mL has been shown to be an independent predictor of postoperative acute kidney injury (odds ratio 1.40, $p < 0.001$). [41] Most importantly, 24-hr CTD is an independent predictor of in-hospital mortality with a linear, ***dose-dependent*** relationship that is independent of blood transfusion requirement. [23]

Key Secondary Endpoints: Evaluation of the change in preoperative to postoperative apixaban and rivaroxaban drug concentrations will be the key secondary endpoints. These drug removal endpoints will quantify the extent of DrugSorb-ATR's apixaban and rivaroxaban removal capabilities, while also providing a mechanistic relationship to the improved surgical and post-surgical bleeding outcomes (i.e., less drug = less bleeding).

Pre-randomization stratification based on a) type of DOAC (either apixaban or rivaroxaban), b) study site, and c) planned operation will address potential confounding effects that may not be fully controlled in the randomization process. Stratification by DOAC type is intended to control for any

unanticipated differences between apixaban and rivaroxaban. Stratification by site is intended to control for institutional differences in standard practices, such as transfusion and re-operation protocols. Stratification by the type of planned operation will separate subjects undergoing CABG-alone from those undergoing all other cardiothoracic surgeries. The category of "all other" cardiac surgeries include combination cases (e.g., CABG + valve, double valve, etc.) and ascending aortic interventions. Compared to CABG-alone, these operations have a significantly different profile regarding bleeding risk and procedure/CPB duration. This distinction is important since device exposure is directly related to the amount of time spent on CPB. Details of the statistical considerations around the endpoints discussed above will be provided in **Section 11**.

In summary, the objective of this randomized, double-blind investigation is to examine the ability of DrugSorb-ATR (a non-pyrogenic, sterile, single-use device designed to remove the small hydrophobic drugs, apixaban and rivaroxaban) to reduce surgical and post-surgical bleeding compared to current standard of care. Measurements of drug removal will be performed to correlate the clinical outcomes (i.e., reductions in bleeding) to reductions in circulating apixaban and rivaroxaban levels. The safety of the device in this setting will be assessed by systematic capture of all AEs at CGP level.

4. INVESTIGATIONAL PLAN

4.1. Study Objective(s)

Patients undergoing cardiothoracic surgery ≤36hrs after last apixaban or rivaroxaban dose are at increased risk of bleeding due to the anticoagulant effect of these medications. The DrugSorb-ATR hemoadsorption cartridge removes circulating apixaban and rivaroxaban at rates much higher than normal washout, thus reversing anticoagulation, improving hemostasis, and reducing surgical and early post-surgical blood loss.

The objectives of this study are as follows:

- To demonstrate reductions in surgical and early post-surgical bleeding with the intraoperative use of DrugSorb-ATR in patients undergoing cardiothoracic surgery with CPB ≤36hrs after last apixaban or rivaroxaban dose;
- To demonstrate reductions in circulating apixaban or rivaroxaban blood levels (Δ[DOAC]) with the intraoperative use of DrugSorb-ATR;
- To establish the safety of the intraoperative use of DrugSorb-ATR in the intended population.

The hypothesis is that, for patients undergoing cardiothoracic surgery with CPB ≤36hrs after last apixaban or rivaroxaban dose, the intraoperative use of DrugSorb-ATR will significantly reduce surgical and early post-surgical bleeding as measured by a ranked composite endpoint of clinically meaningful bleeding metrics: 1) fatal bleeding occurring within 48hrs post operation, 2) moderate, severe, or massive bleeding events based on the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) ≥2 classification, and 3) 24-hour chest tube drainage (CTD).

4.2. Study Design

This will be a prospective, multi-center, randomized, double-blind clinical study. Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) or standard of care plus intraoperative treatment with DrugSorb-ATR.

4.3. Study Outcomes

4.3.1. Primary Effectiveness Endpoint:

- Ranked composite of surgical and early post-surgical bleeding events:
  1) Fatal bleeding events occurring within 48hrs post-index procedure,
  2) UDPB ≥2 perioperative bleeding, and
  3) 24-hour chest tube drainage volume (mL).

Refer to **Table 1** for details of the UDPB classification of bleeding events.

4.3.2. Key Secondary Effectiveness Endpoints:

- Percent change in pre-CPB vs. post-CPB blood apixaban levels as measured by liquid chromatography/tandem mass spectrometry (i.e., Δ[Apixaban]).

- Percent change in pre-CPB vs. post-CPB blood rivaroxaban levels as measured by liquid chromatography/tandem mass spectrometry (i.e., Δ[Rivaroxaban])

4.3.3. Additional Secondary Effectiveness Endpoints:

- 24-hour chest tube drainage volume
- Total platelet transfusions during the index hospitalization (volume and units)
- Total PRBC transfusions during the index hospitalization (volume and units)
- Total UDPB events (by class)
- All surgical re-exploration for excessive bleeding
- Total fatal perioperative bleeding events

4.3.4. Exploratory Endpoint(s):

- Area under the concentration time curve (AUC), for intraoperative apixaban or rivaroxaban pharmacokinetic (PK) concentration
- Operative time (measured from start of skin incision to completion of chest closure)
- Duration of ICU stay
- Duration of hospital stay
- 30-day hospital readmissions

4.3.5. Primary Safety Endpoint:

- The primary safety endpoint of this trial is to evaluate the product safety profile through the GCP-level assessment of AEs during the study period.

4.3.6. Additional Safety Endpoints:

- 30-day cardiac mortality
- 30-day all-cause mortality
- Postoperative stroke during the index hospitalization
- Postoperative myocardial infarction (MI) during the index hospitalization
- Urgent postoperative coronary revascularization during the index hospitalization
- Postoperative venous thromboembolic events (VTE) during the index hospitalization
- Serious device-related adverse events

4.4. Subjects and Selection of Study Population

Subjects must meet all inclusion criteria to be eligible to participate in the study. Subjects meeting any of the exclusion criteria are not eligible to participate in the study.

4.4.1. Inclusion Criteria:

1. Males and females aged ≥18
2. Written full informed consent
3. Undergoing cardiothoracic surgery with CPB ≤36 hours following last dose of apixaban or rivaroxaban.

Only patients taking apixaban or rivaroxaban for one of the following indications are eligible for enrollment: a) reduction of stroke/systemic embolism in nonvalvular atrial fibrillation, or b) initial or extended treatment of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

4.4.2. Exclusion Criteria:

1. Cardiothoracic surgery >48 hours after last known dose of apixaban or rivaroxaban
2. Patients on low dose apixaban or rivaroxaban for prophylactic indications (e.g., DVT prophylaxis after hip/knee replacement surgery, or risk reduction of major CV events in patients with CAD/PAD)
3. Heart-lung transplant procedures
4. Procedures for ventricular assist device (i.e., implant or revision of LVAD or RVAD)
5. Any of the below conditions that pose a known risk for increased bleeding:
    a. Heparin induced thrombocytopenia
    b. Preoperative platelet count < 50,000 / μL
    c. Hemophilia
    d. INR ≥ 1.8
6. Prohibited concomitant antithrombotic medications (reference Appendix 5)
7. Acute sickle cell crisis
8. Known allergy to any of the device components
9. Subjects with active (untreated) systemic infection
10. Subjects with a history of major organ transplantation and those currently receiving immunosuppressive medication (corticosteroids excluded) or who are profoundly immune suppressed
11. Women of childbearing potential with a positive pregnancy test performed during the current admission or who are breast-feeding
12. Subjects with life expectancy of <30 days (not inclusive of the critical condition that is requiring the cardiac operation under study for which there is a reasonable expectation that cardiac surgery with the device may prolong life for more than 30 days)
13. Inability to comply with the requirements of the study protocol
14. Treatment with an investigational drug or device within 30 days prior to surgery
15. Subjects with previous enrollment in this trial

4.4.3. Informed Consent & Enrollment Procedures:

Informed consent shall be obtained in writing from the subject, or their legally authorized representative and the process shall be documented before any procedure specific to the clinical

investigation is applied to the subject; additional details are provided in Appendix 3. If during the course of the study assessments, a subject is found not to be eligible for inclusion in the study, the subject or their representative should be notified and the reason for ineligibility documented on the screening log/form.

The general process for obtaining informed consent shall:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive the subject's legal rights
- Use native non-technical language that is understandable to the subject
- Provide ample time for the subject to read and understand the Informed Consent Form (ICF) and to consider participation in the clinical investigation
- Include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process;
- Provide the subject with a copy of the signed and dated ICF and any other written information
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation

4.4.4. Subject Withdrawal/Discontinuation:

Investigation subjects may withdraw voluntarily from the research investigation for any reason and at any time during the course of the investigation. Subjects may also be discontinued from the investigation for the following medical or administrative reasons:

- At the request of the Investigator, if he/she feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the subject.
- Termination of the study by the Sponsor.
- Non-compliance with CIP procedures.
- The subject is lost to follow-up. A subject will be considered "lost to follow-up" when all the following criteria are met:
    - Failure to complete the 30-day follow-up visit or follow-up telephone call without due cause; and
    - Documentation of three unsuccessful attempts to contact the subject via telephone and/or by certified mail.

If a subject is withdrawn from treatment, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). For subjects who withdraw assent/consent and those withdrawn at the request of the Investigator, details of the reason for withdrawal will be captured to the extent possible. If a subject is withdrawn, efforts will be made to perform all follow-up assessments, if possible. Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. The Investigator (or designee) may also request that the subject return for an additional Follow-up Visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to investigation treatment may be replaced following discussion between the Investigator and the Sponsor. For subjects who withdraw or discontinue at any point prior to completion of the required follow-up period, all available data will be used in the analysis, following the intent-to-treat principle. In cases where analysis criteria are not met, for example for the Per Protocol population, such subjects may not be included in the analysis. Subjects withdrawing or discontinuing early will be summarized as described in **Section 11.8**, and will be flagged in a listing of disposition information that includes reason for early withdrawal/discontinuation.

5. POTENTIAL RISK/BENEFIT

5.1. Potential Investigational Device Risks

DrugSorb-ATR is a hemoadsorption cartridge that is incorporated into an extracorporeal CPB circuit. For the study described in this protocol, use of DrugSorb-ATR will be limited to the duration of CPB. The risk profile associated with DrugSorb-ATR is expected to be consistent with other extracorporeal treatments currently in clinical use. Potential risks associated with the use of the device are described below.

Risks Specific to DrugSorb™-ATR:

- Removal of therapeutic drugs <60kDa in size, that contain hydrophobic or aromatic moieties.
- Removal of endogenous, non-pathogenic, physiologic substances from the blood: A risk of removal of substances ≥900Da – 60kDa in size; this risk is greater the longer DrugSorb-ATR hemoperfusion is performed on a subject.
- Hemolysis (if maximum recommended flow rate per the IFU is exceeded).
- Allergic response to device materials.
- Device leakage.
- Death.

Risks commonly associated with extracorporeal therapies themselves will not be detailed here, however such risks would also apply to the DrugSorb-ATR device, given its incorporation into these circuits.

5.2. Potential Benefits

The observed and potential benefits of using DrugSorb-ATR intra-operatively during cardiothoracic surgery to remove apixaban and rivaroxaban include:

- Decrease in surgical and post-surgical bleeding complications, including:
    - Decrease in intra-operative blood loss
    - Decrease in post-operative blood loss, including that measured in chest/mediastinal drains
    - Decrease in blood product transfusions
    - Reduced risk of re-operation for bleeding
    - Reduced risk of fatal bleeding
- Improvement in hemodynamic stability and reduction in vasopressor requirements, as a result of decreased bleeding

5.3. Risk Mitigation

Mechanical and performance concerns have been reduced by extensive human, animal, and bench

testing. The device materials have been shown to be biocompatible and acceptable for human use through ISO10993 testing and prior human clinical studies of the device for removal of beta-2 microglobulin in subjects with end stage renal disease and removal of cytokines in the treatment of sepsis. The DrugSorb-ATR cartridge has CE Mark approval under the name of CytoSorb® for removal of ticagrelor and/or rivaroxaban in subjects undergoing emergent cardiothoracic surgery with CPB and is believed to pose minimal additional risks compared to standard CPB circuits without DrugSorb-ATR. Those risks and their mitigation strategies are presented in **Table 2** below.

DrugSorb-ATR does not remove heparin or citrate, and therefore does not impact heparin- or citrate-mediated anticoagulation during CPB. Adherence to protocol will be stressed by CytoSorbents' personnel during in-service training. All subjects will be monitored per routine standard of care. Additionally, the Data and Safety Monitoring Board (DSMB) will be reviewing safety information on an ongoing basis, thus providing an additional level of risk mitigation.

Table 2. Risks and Mitigation Strategies

Potential Device/Intervention Risk	Action for Risk Mitigation
Risk of coagulation within the device or the CPB circuit, and associated thromboembolic events (e.g., stroke, peripheral embolus, etc.)	Visual inspection for signs of coagulation within the device or the circuit during CPB on a regular basis. Constant supervision during the CPB procedure.
Removal of drugs (such as antibiotics) and hormones	If a drug(s) is known to have high likelihood of removal by DrugSorb-ATR, and a selective test is available for that drug(s), the treating physician is recommended to check the concentration of applied drugs following CPB and adapt the dosages accordingly. This theoretical risk is greater, the longer DrugSorb-ATR hemoperfusion is performed on a subject. Therefore, it would be anticipated that this risk would be acceptable when device exposure is limited to the brief intraoperative period with CPB.
Allergic/ anaphylactic response to device materials	Subjects with known allergies against device materials (including but not limited to ***polystyrene/divinylbenzene, polycarbonate, polypropylene, silicone, and polyester***) will be excluded from the study. If applicable, in subjects manifesting unexpected signs of allergic reaction during therapy with DrugSorb-ATR, the exposure will be discontinued immediately. In addition, aggressive first-line therapy shall be applied to control the allergic or anaphylactic reaction.
Risks related to blood composition: • Reduction in platelet count • Reduction in white blood cell count • Reduction in proteins (albumin or total protein) • Hemolysis	Close monitoring of blood parameters prior, during, and after extracorporeal therapy according to the prescribed routine (reference the Schedule of Assessments in **Table 6**) Flow through the device will be monitored closely through-out the procedure. The DrugSorb-ATR device maximum flow rate has been validated for hemolysis, and there are no independent risks *associated with the maximum recommended flow rate* of the DrugSorb-ATR device.

Impairment of device function (DrugSorb-ATR and CPB) in combination with parenteral nutrition (most notably: lipid emulsions)	In case of needed artificial nutrition, gastric application or other-than-parenteral application shall be preferred. In case of need for parenteral application of lipid-containing nutrition, it is recommended to postpone the application only after the procedure or to stop the application at least two hours prior to the CPB-procedure.
Bleeding events due to necessary anticoagulation with CPB and DrugSorb-ATR use	Constant supervision of coagulation parameters during the procedure, in accordance with standards of care.
Infection	DrugSorb-ATR is sterile and is delivered in sterile packaging. The packaging will be checked for possible damage before use. Products with visible defects will not be used and will be reported to the Sponsor.
Blood loss	Return of the blood sucked from the surgical field to the CPB circuit (i.e., Cell Saver) for reduction of blood loss. Constant supervision of the extracorporeal circuit for blood loss through-out the procedure.
General complications within in context of extracorporeal therapies (including but not limited to): • Dyspnea • Hypoxia • Changes in body temperature • Muscle cramps • Headache • Nausea • Vomiting • Pruritus	Constant supervision of the subject during and after the CPB-procedure. Designation of personnel duly trained in the use of extracorporeal therapies.
Device or circuit leakage	Visual inspection for signs of leakage within the device, or the circuit during the CPB-procedure on a regular basis.
Unwanted penetration of air into the extracorporeal circuit, and risk of associated events such as pulmonary embolism and death due to pulmonary embolism	Checking of connections, lines, and circuit components for integrity of the system, and use of appropriate precautions to avoid introduction of air into the system when incorporating the device into the circuit. The device will be setup in a standardized configuration under positive pressure; the volume will be returned to the reservoir pre-pump and pre-oxygenator membrane, thus essentially eliminating risk for air introduction to the patient. Constant supervision of the subject during the CPB-procedure.

6. STUDY TREATMENT

All treatments will be provided by trained professionals. Use of DrugSorb-ATR will follow the Instructions For Use (IFU) under the guidance and/or training of a Field Clinical Specialist.

6.1. Pre-randomization Stratification

Pre-randomization stratification will be performed on three levels, based on the rationale described below:

1. By preoperative DOAC type (either apixaban or rivaroxaban), to control for unanticipated differences between component drugs

2. By study site, to control for differences in institutional protocols for bleeding and transfusion management. Institutions may also differ in metrics utilized for clinical decision-making (e.g., decision to delay sternal closure, or surgical reoperation).

3. By the intended surgical procedure, to control for differing procedure-specific bleeding risks, and duration of CPB (i.e., device exposure) as detailed below:

    - CABG alone (irrespective of number of grafts); or

    - All other cardiothoracic procedures including but not limited to combination procedures (i.e., CABG + aortic/mitral valve procedures, double heart valve procedures, etc.), aortic interventions, and combination aortic + cardiac interventions. These surgeries generally require longer CPB time than CABG alone.

Of note, during the pre-procedure and intraoperative periods, the intended procedure may change due to factors that could not be adequately anticipated in advance of the procedures. These day-of-surgery changes to the planned operations may result in the completion of a procedure that a) does not align with eligibility criteria, or b) alters stratification. Any change to the intended procedure occurring on the day of surgery that is not updated in the final IxRS assignment will be considered a protocol deviation. These protocol deviations will be noted in a deviation log for data analysis considerations at the conclusion of the trial. All subjects who have any of the above changes to their intended procedures should progress through the study as per the protocol.

6.2. Subject Randomization

All subjects will be prospectively randomized via an Interactive Voice/Web response (IxRS) system. Randomization must occur prior to the start of the cardiothoracic surgery procedure requiring CPB, but only after subject eligibility criteria is confirmed and written informed consent is provided by the subject or the subject's legally authorized representative/designated proxy. Subjects will be randomly assigned in a one to one (1:1) ratio to either the control arm (SOC) or the investigation arm (SOC + DrugSorb-ATR).

To ensure even distribution of subjects among the factors most likely to impact the primary and secondary outcomes, they will undergo pre-randomization stratification based on DOAC type, study site, and type of CT surgery. Neither the investigator nor the subjects will be told their assignment prior to surgery. See below (**Section 6.3.1**) for details of the randomization assignment. A copy of the randomization assignment will be maintained in a confidential file maintained by the Randomization and Unblinding Administrator. If the subject withdraws consent following randomization but prior to surgery, the reason for failure to treat according to randomization will be recorded in the subject's

study records.

To maintain the balance between sites in terms of numbers of subjects randomized, study sites will be capped at randomizing a maximum of 15% of the overall study sample (i.e., 18 subjects). Sites may be allowed to randomize beyond the cap on a case-by-case basis in consultation with the sponsor, considering overall study goals, randomization balances between sites, and prior quality of data collected by the site. For sites with a total enrollment consisting of only one type of the two eligible DOAC drugs, the randomization cap will be replaced by a maximum of 10% of the overall study sample (i.e., 12 subjects). In order to maintain the study-wise ratio of apixaban vs. rivaroxaban subjects within planned limits (a range of anywhere between 40% - 60% for each), the IxRS system will be used to limit enrollment accordingly.

6.3. Blinding

Blinding of the study subjects and site personnel (e.g., Surgeon, Anesthesiologist, operating room staff, study coordinator) to treatment assignment is implemented starting at the point of randomization and extending through the duration of the entire study. Accordingly, the blinding procedure will minimize any potential bias in both surgical and postoperative care decisions that may be introduced by knowledge of treatment assignment.

Each site will assign an unblinded perfusionist to execute the necessary intraoperative study procedures. Extreme caution should be exercised by the perfusionist to prevent inadvertently revealing treatment assignment to individuals making clinical decisions on subject care.

The unblinded perfusionist at the site will ensure the placement of a barrier that covers the device/sham set-up from view of the surgical staff. A Field Clinical Specialist, as designated by the Sponsor, may be present to assist with set up of the blind and provide guidance during the procedure. Details on the roles and responsibilities of the Sponsor FCS are provided in **Section 6.4**.

6.3.1. *Maintaining the Study Blind*

The following describes the measures being taken to maintain the study blind:

a) **Subjects:** Subjects will not be told their randomization assignment by any site study personnel involved in the trial and will receive the same care throughout the trial.

b) **Randomization Assignment:** Each site will randomize subjects using an Interactive Voice/Web response (IxRS) system. After the appropriate information is entered, an assignment is made (Standard of Care vs. Standard of Care + DrugSorb-ATR). This randomization process is performed by the unblinded team prior to the procedure.

c) **Site Study Personnel:** There are two designated teams at each site:

1. **Blinded**: These individuals remain blinded from the point of randomization through the duration of the study, inclusive of all subjects enrolled at the site. Responsibilities of blinded site personnel are detailed below.

   - Surgical team (including the surgeon, surgical assistant, circulating nurse, scrub tech, and other operating room staff);
   - Anesthesiologist and anesthesia team;
   - ICU staff;
   - Study coordinator.

2. **Unblinded**: These individuals will be aware of treatment assignment and will refrain from revealing it to any other study personnel for the duration of the study, inclusive of all subjects enrolled at the site. Additional responsibilities are detailed below.

    - Perfusionist(s);
    - Sponsor FCS.

The **Blinded Team** is responsible for administering all pre-, intra- and post-procedure subject testing and care as designated by the protocol. The blinded site study coordinator(s) will be responsible for data entry into the EDC, including input of follow-up visit data into the relevant eCRF. The blinded study coordinator will also be responsible for ensuring required follow-up care/visits for all study subjects are scheduled; The Sponsor will work with each individual site to determine the documentation needed in the subjects' medical records (e.g., procedure notes) to protect the study blind.

The **Unblinded Team** is responsible for activities related to the procedure, including set-up of the device according to randomization assignment (sham or DrugSorb-ATR), oversight of the device during the procedure, and recording the device study data (e.g., device lot number, start/stop time of flow through the device, device flow rates, and any device quality complaints) in the eCRFs and device accountability log. Other responsibilities include:

1. Obtaining a randomization code from the electronic system prior to the index procedure, including day of procedure;
2. Ensuring appropriate device cartridges are available and in the OR suite on procedure day;
3. Providing necessary procedure information in a blinded fashion to the study coordinator for eCRF entry.

6.3.2 Study devices

All study devices will be blinded by coverage with a sterile drape. For subjects randomized to DrugSorb-ATR, the unblinded perfusionist will monitor flow to ensure it stays within the protocol dictated range.

Subjects randomized to standard of care without DrugSorb-ATR (i.e., control) will have a ***sham device*** in the operating room. The sham device is identical in appearance to an active DrugSorb-ATR cartridge. Sham devices are sealed, inactive, pre-assembled device sets containing liquid to mimic a primed, ready to use, device. They are permanently sealed and cannot be put online with the perfusion circuit. Sham devices are marked **"Not for human use"** and cannot be opened, and they will not support flow, as they are glued/sealed shut. These devices are clamped like the DrugSorb-ATR device, but line connections are not made to the CPB circuit. Once installed, the sham device is covered with a sterile drape, and tubing lines approximate the positioning of the real DrugSorb-ATR device.

Assembly of the blind space may be required in advance should the OR personnel be in the workspace during set-up, to preserve knowledge of treatment allocation. The FCS and/or unblinded perfusionist ensures the blind is maintained prior to, throughout, and post-surgery. Of note, the sham device and blinding scheme discussed above is identical to the model used

in STAR-T, which is an ongoing IDE study already approved by the FDA.

6.3.3 Unblinding Procedure

It is the intention of this study to unblind both the subject and the site study personnel at the completion of the overall study. This will occur **after** all necessary 30-day follow-up assessments are completed and all the data have been collected and verified for all subjects, and the clinical database has been "locked", or write-protected from further changes. If the subject develops a condition within the 30-day follow-up window, the subject and team will be unblinded ***only if doing so is necessary to make informed decisions about clinical care, or in the possibility of an unanticipated adverse device effect (UADE)***.

Any subject that is unblinded prematurely for any reason shall continue to be followed in accordance with the protocol evaluations outlined. A subject is NOT automatically considered to be withdrawn if unblinding occurs earlier than anticipated.

If the site investigator believes there is reason to unblind either themselves or the subject (e.g., significant change in subject's health status related to the possible use of the device), the site will contact the Sponsor to discuss the subject's circumstances, at which time the Sponsor, if in agreement with the site's request, may approve release of the blinding information by the unblinded Sponsor designee.

6.4. Field Clinical Specialists

Support by a Field Clinical Specialist (FCS), as designated by the Sponsor, may be offered to assist with set up of the blind and provide guidance during the procedure. In instances where the Sponsor-designated FCS has previously observed set-up of the investigational device and has found the unblinded perfusionist(s) skilled and competent to manage study procedures, a waiver of FCS assistance may be granted. All such waivers of FCS assistance will be documented and retained in the study file.

The FCS will observe and proctor the unblinded perfusionist as he or she assembles the DrugSorb-ATR cartridge and peripheral FDA-approved components as specified in the IFU. The unblinded perfusionist is responsible for the final hookup to the hospital perfusion apparatus. The Sponsor FCS will be available through-out the procedure to provide additional support to the perfusionist as needed. This approach is consistent with site expectations for study support and will further ensure study subject safety in a novel device trial. In addition, the presence of the FCS will likely reduce variability in study related procedures and ensure their timely execution (i.e., serial blood sampling for drug levels).

6.5. Device Quality Complaints: Deficiencies, Malfunctions, and Observations

If there is a device deficiency, malfunction, or other observation with the DrugSorb-ATR device (i.e., device quality complaint) the Investigator (or designee) is required to complete the Device Deficiency/Observation eCRF and to notify the Sponsor immediately and indicate if the observation resulted in an adverse event and indicate if complications are related to the device, procedure, or underlying disease. If the device quality complaint is associated with an SAE, SADE, or UADE, the Investigator will be required to enter the adverse event within 24hrs of awareness, and this information will be transferred to the Contract Research Organization (CRO) and Sponsor through automated notification.

In the event of any suspected device problem, the device shall be returned to the Sponsor for analysis.

Instructions for returning the investigational device are included in the Study Reference Manual. If the investigator cannot determine the cause of the event, it should be classified as unknown.

7. STUDY OVERSIGHT

7.1. Data and Safety Monitoring Board (DSMB)

This is an independent committee that will be charged with ensuring the safety of the subjects enrolled in the clinical study. The Data Safety Monitoring Board (DSMB) will be comprised of four members: three clinicians and one biostatistician with relevant clinical/medical experience with the indication/disease under clinical investigation. The membership of the committee will be independent of the investigative sites and study sponsor to reduce potential for perception of bias and to remain free of potential conflicts of interest. The policies and procedures governing the DSMB will be provided in a Charter that will be reviewed and ratified by the membership within a reasonable timeframe relative to the enrollment of the first few subjects entering the study.

Included in the charter will be a mission statement, operating procedures, proposed monitoring criteria, time points for interim analysis, and proposed stopping rules if appropriate. There will be at least 4 DSMB meetings during the trial: a kick-off meeting of the DSMB in proximity of the start of enrollment, and 3 safety reviews scheduled at 33% study completion, 70% study completion (corresponding to the Interim Analysis), and a final review after database lock. The DSMB will meet at a minimum once per 6 months if a meeting is not already triggered by the above scheduled enrollment timeframes. Written recommendations from the DSMB will be provided to the study sponsor following each safety review meeting. The DSMB will operate under the auspices of an academic research organization.

7.2. Clinical Events Committee (CEC)

An independent group of physicians that are not involved in the clinical investigations will act as the Clinical Events Committee (CEC). The CEC will be responsible for the review and adjudication of study effectiveness and safety endpoints that occur within 30 days post-operation according to standardized definitions. Policies and procedures governing the work of the CEC and the definitions used in the adjudication process will be provided in the CEC Charter, which will be developed prior to the start of study enrollment. The CEC will operate under the auspices of an academic research organization.

7.3. Executive Committee

This committee shall serve as overall governance of the trial and will be comprised of clinicians with relevant clinical/medical experience within the indication/disease under clinical investigation and who also have significant experience in overseeing clinical studies. The Executive Committee shall provide advice to the Sponsor regarding the conduct and any necessary adjustments to the trial protocol and/or study execution. The Executive Committee will also advise the Sponsor in the case that any decisions are necessary in response to recommendations provided by the independent Data and Safety Monitoring Board.

7.4. Central Laboratory

A central laboratory shall be utilized to analyze some of the blood samples collected in this study. The sample size and shipping requirements are provided to the sites in the Study Laboratory Manual. All sites will be trained on the collection, preparation, and shipping for central laboratory samples.

8. STUDY MONITORING

The CRO will monitor and manage the data for the investigational study on behalf of the Sponsor, CytoSorbents, Inc. A study-specific Monitoring Plan will be created to ensure protocol compliance and adherence to applicable regulatory requirements. The monitoring process will begin with site initiation activities and continue until completion of the study closeout visit. Clinical monitors will verify subject data and ensure compliance is consistent with Good Clinical Practice (GCP), clinical protocol and other study requirements, according to the guidelines per the Monitoring Plan, set forth in the CROs monitoring Standard Operating Procedures (SOPs), and 21 CRF Part 812.

8.1. Monitor Training

The designated monitors and/or representatives of the Sponsor will be trained to monitor study progress including but not limited to the protocol and eCRFs, and per the Monitoring Plan.

8.2. Site/Investigator Training

The Sponsor is responsible for providing training to the Investigator and appropriate clinical site personnel on the following topics:

- Protocol
- Electronic case report form (eCRF) data entry and management
- Procedure/Laboratory/other testing requirements
- DrugSorb-ATR device

8.3. Site Monitoring

Completed eCRFs will be verified by the monitor both in person at the investigational sites and remotely at regular intervals throughout the study. The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, subject eCRFs, subject medical records and other related study documents as required. All eCRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified, and entered by study personnel as necessary throughout the study. CytoSorbents, Inc., or their authorized representative may request additional documentation from the Investigator such as physician procedure notes or physician written summaries when adverse events are observed and reported.

8.4. Regulatory Agency Inspection

If an Investigator is contacted by a regulatory agency regarding this study, the Investigator will notify the Sponsor or its designee immediately. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The Investigator must provide the Sponsor or designee with copies of all correspondence that may affect the review of the current trial (e.g., Form FDA 483, Inspectional Observations and Warning Letters). The Sponsor may provide needed assistance in responding to regulatory audits.

9. STUDY ASSESSMENTS AND PROCEDURES

An outline of study assessments, procedures, labs, and associated time windows is given in the **Schedule of Assessments** (**Table** 6 in Appendix 4). Subjects will be evaluated through the Follow-up evaluation at 30 days post-operation. Assessments and procedures that are recorded as Standard of Care (SOC) within the **Schedule of Assessments** are outside of the CIP and are optional. They may be recorded if they are performed in accordance with SOC at the particular institution. Failure to record an assessment/procedure that is listed as SOC will not be a violation of protocol. Required assessments and procedures (not denoted as SOC) that are not completed or that are completed outside of the specified windows will be recorded as a protocol deviation (**Section 13.2**, **13.3**).

Reference **Section 4.3** for the full list of study endpoints. These endpoints require assessment of clinical events and/or treatments, blood product transfusions, drainage volume, and laboratory parameters. Definitions of analysis populations and description of statistical analyses of endpoints are briefly described in **Section 11** and will be detailed in the Statistical Analysis Plan (SAP) for the study.

9.1. Procedures and Assessments by Study Phase

Subjects are considered enrolled in the study at the time which consent or assent (in the case of a proxy providing permission for an incapacitated subject) to participate in the study is provided. Details on the consent process are provided in **Section 15.3** and the ethics of consenting non-vulnerable and vulnerable (incapacitated) populations are detailed in Appendix 3.

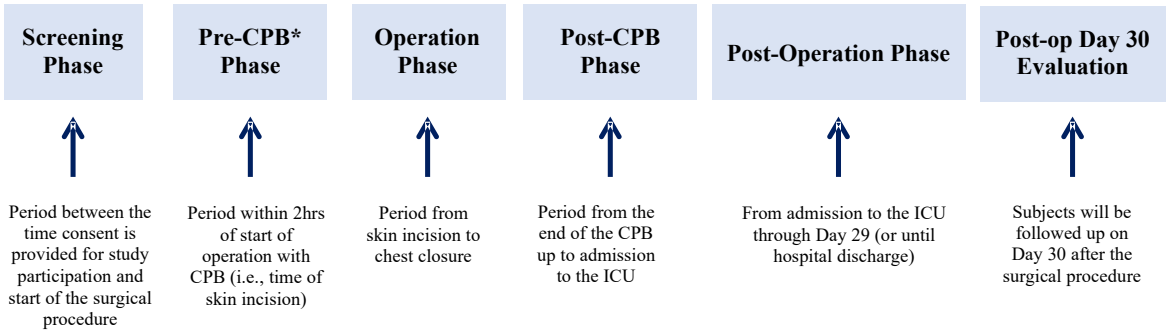
Subjects who do not meet study entry (inclusion/exclusion) criteria are screening failures and will exit the study. Treated subjects will be followed up through 30 days after the surgical procedure.

The start of the investigation is defined as the date of consent to enroll the first prospective subject. The end of the investigation is defined as the date of the last subject's last contact or assessment (whether scheduled or unscheduled).

The investigation is divided operationally into 6 phases:

- Screening Phase – the period between the time consent/assent is provided for study participation and the start of the surgical procedure with CPB
- Pre-CPB Phase – the period within 2 hours before start of the operation with CPB (time of skin incision). *Note: The Pre-CPB Phase may overlap with the Screening phase.*
- Operation Phase – the start of the surgical procedure (defined as skin incision) until chest closure.
- Post-CPB Phase – the period from the end of CPB up to admission to the Intensive Care Unit (ICU). *Blood sampling for drug removal obtained in the post-CPB phase should be drawn as soon as possible following the end of CPB, and no later than 30min after the subject has been disconnected from the CPB circuit.*
- Post-operation Phase – from admission to the ICU through Day 29 or the point of discharge from hospitalization, whichever is sooner. ***Discharge from hospitalization*** means the date of initial discharge from the hospital in which the cardiothoracic surgery was completed (i.e., index procedure) irrespective of discharge to home care, secondary care or other rehabilitation unit.
- Day 30 Evaluation Post-Cardiothoracic Surgery – The subject status on postoperative day 30 will be evaluated by telephone contact, in-person follow-up visit, or review of medical records. Assessment of mortality (i.e., vitals status), blood product transfusions, and other adverse events will be performed.

An overview of the investigation design is shown in **Figure 5**.



* Pre-CPB phase may overlap with the Screening Phase.

Figure 5. Investigation Schematic

9.1.1. Screening Phase and the Pre-CPB Phase

The Screening Phase through the Pre-CPB Phase is the period bound by the time that consent is provided for study participation and the start time of CPB. Subjects are qualified for study participation by confirmation of meeting all the inclusion and none of the exclusion criteria.

Each enrolled subject will be assigned a unique Subject Number consisting of a Site Number assigned by the Sponsor or designee, and a number which is sequentially assigned to all subjects screened at the investigation sites (e.g., XXX-YYY, where XXX is the site number and YYY is the subject number). The Subject Number will be used as a subject identification for each subject throughout the investigation.

Screening and pre-CPB assessments should be completed as detailed in **Table 6**. As discussed in **Section 1.1,** all subjects undergoing CABG or with recent coronary stent placement (within prior 6 months) should have aspirin continued going into surgery. An overview of antithrombotic and anticoagulation management for study subjects is provided in Appendix 4, **Table 5**. During Screening, if consented subjects enter the Operation Phase without ***post-consent*** clinical chemistry, cardiac troponin, hematology, or coagulation tests to record, the last pre-consent laboratory values MAY be used.

Pre-randomization stratification

Pre-randomization stratification will be performed on three levels (see **Section 6.1** for details):

1. By DOAC type (either apixaban or rivaroxaban);
2. By study site;
3. By the planned surgical procedure:
   - Isolated CABG (irrespective of number of grafts); or
   - All other cardiothoracic procedures requiring CPB.

Randomization

Subjects will be prospectively randomized in a one to one (1:1) fashion to either the control arm (SOC) or to the investigation arm (SOC + DrugSorb-ATR), as detailed in **Section 6.2**.

9.1.2. Operation Phase

The Operation Phase will be initiated at the time of first incision. During the Operation Phase, the subject will either undergo standard CPB, or CPB + DrugSorb-ATR according to randomization.

Subjects randomized to the control arm will receive standard of care in which a sham device will be in place parallel to the CPB circuit, but through which no blood will circulate. Refer to **Section 6.3** for details.

In the treatment arm, DrugSorb-ATR treatment will initiate with the start of CPB and continue through the end of CPB. Per the IFU and under the guidance of a Field Clinical Specialist, the DrugSorb-ATR cartridge will be placed into a parallel bypass circuit to the main blood flow in a standard CPB circuit and primed for use in preparation for the Operation Phase. Throughout the treatment session, the DrugSorb-ATR setup will be monitored for blood leaks, flow changes, and/or clots. Any adverse device events and/or device observations must be recorded by indicating the location of leaks and/or by recording the size of any clots present. DrugSorb-ATR treatment flow rates will be controlled utilizing a roller clamp placed on the distal, superior line above the DrugSorb-ATR prior to returning to the reservoir. Flow rate will be measured using a Sponsor provided Transonic® (or equivalent) ultrasonic flow meter and probe, placed on the inlet line below the DrugSorb-ATR device. **The blood flow rate through the device will be adjusted to 500mL/min ± 100mL/min**.

During the operation phase, arterial blood gas analysis will be obtained at the following time periods: within 30min pre-CPB, 30 ± 15 min into CPB, within 30 minutes post-CPB, and upon admission to the ICU. Activated clotting time will be obtained once at 30 ± 15 minutes into CPB, and once *within 30 minutes* post-protamine administration. All other assessments including monitoring of transfusions, will be performed as detailed in **Table 6** of Appendix 4. Intraoperative transfusions will be administered at the discretion of the investigator in accordance with standard institutional practice.

9.1.3. Postoperative phase through 30-day evaluation

Subjects will undergo scheduled study procedures as indicated in the Schedule of Assessments in Appendix 4 until the point of discharge from index hospitalization. A Follow-up Evaluation will be performed 30 days after the index operation for vital status/mortality check. This can be done via telephone contact, in-person follow-up visit, or review of medical records.

Postoperative Antithrombotic Management:

Approaches to antiplatelet and anticoagulation management during the study are listed below and summarized in **Table 5**. All subjects on preoperative aspirin should be maintained on the same therapy through-out the study. Additionally:

1. Any ACS subjects or those with recent coronary stent placement who ***cannot*** discontinue DAPT (i.e., clopidogrel, ticagrelor, etc.) for the recommended ***preoperative washout*** period will be excluded from study participation. Initiation of DAPT in the ***postoperative*** period is at the discretion of the investigator, or per their institutional protocols.
2. Timing of resumption for DOAC therapy in the postoperative period will be at the discretion of the investigator, based on the indication for anticoagulation and the anticipated bleeding risk.

Postoperative anticoagulation for venous thromboprophylaxis in all subjects should be administered according to standardized institutional protocols.

9.2. Safety and Tolerability Assessments

9.2.1. Adverse Events

Throughout the study, the Investigator or designee will determine adverse event (AE) occurrences. AE definitions, assignment of severity/seriousness/causality, and procedures for reporting SAEs, SADEs, and UADEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the Informed Consent Form (*assent* if signed by the legally authorized representative, or *consent* if signed by the individual) to the postoperative day 30 assessment. Subjects will be observed for any signs or symptoms and if possible, asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at least once each day while in hospital and at each investigation visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the investigation.

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the investigation treatment may be discontinued if deemed clinically necessary. Follow-up evaluations of the subject are to be performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant.

Adverse events are monitored and recorded on the AE form of the eCRF. In absence of a specific diagnosis, an individual AE form must be filled in for each sign or symptom. Changes from baseline laboratory values which are abnormal values and that are classified as clinically significant by the investigator (e.g., requiring medical intervention) must be recorded as AEs.

Persistent AEs will be entered once in the eCRF until they are resolved; a new event must be documented if deterioration occurs. These AEs will be carefully monitored. If an AE is still not resolved at the end of the investigation, this will be documented as "ongoing." For recurrent AEs (i.e., AEs of the same nature, but with a different date of onset), an individual AE form must be completed for each of them.

Bleeding event AEs
All bleeding events are to be recorded as AE/SAEs by the Investigator or designee. Volume of blood loss and necessary transfusions will be documented in the corresponding eCRFs where applicable. In some cases, these events may contribute to the subject's UDPB class. [35] Classifications are based on criteria/events occurring within the first postoperative day (as presented in **Table 1**) and will be determined based on the relevant data entered within the eCRFs.

Of note, UDPB counts transfusions of PRBCs, platelets, FFP, and Cryoppt beginning at chest closure. While intra-operative transfusions of these blood products prior to chest closure will be documented, they will not be counted as part of the UDPB classification or contribute to the primary endpoint. Preoperative transfusions are not counted in the UDPB classification. Transfusions of PCC and rFVIIa are counted beginning at the start of the procedure for UDPB. [35] Measurement of CTD volume begins at chest closure for UDPB classification. All subjects with events meeting criteria for UDPB classification of moderate, severe, or massive bleeding (Classes 2, 3 or 4) will be referred to the CEC for adjudication of UDPB bleeding class. Bleeding events occurring beyond the first postoperative day (i.e., not eligible for UDPB classification) will be adjudicated by the CEC for clinical severity. Details on the process for adjudication and relevant definitions are provided in the CEC Charter.

Postoperative Ischemic Events:

Postoperative ischemic events occurring during the index hospitalization will be captured as safety

endpoints in this study. This is with the intent of evaluating any potential risk for ischemic rebound in the setting of rapid antithrombotic drug removal. Postoperative ischemic events include myocardial infarction (MI), stroke, and urgent coronary revascularization. Of note, given the occasional complexities of distinguishing ischemic from hemorrhagic stroke (i.e., ischemic with hemorrhagic conversion), *all* postoperative strokes occurring during the index hospitalization will be captured within the safety endpoint.

All reported safety events occurring within 30 days of the study procedure that meet programed criteria for cardiac ischemia or stroke will be submitted to the CEC for endpoint adjudication. All coronary revascularization procedures (regardless of open or percutaneous) that occur post-index procedure and during the follow-up period will be adjudicated by the CEC for the potential safety endpoint of *urgent coronary revascularization*. Details on endpoint definitions, adjudication criteria, and all other CEC processes/procedures are detailed in the CEC charter.

Venous Thromboembolic Events:

Postoperative venous thromboembolic events (VTEs) occurring during the index hospitalization will also be captured as safety endpoints in this study. These include clinically significant deep vein thromboses and pulmonary embolism. The intent is to identify any potential risk for thrombotic rebound in the setting of rapid anticoagulant removal.

All reported safety events occurring within 30 days of the study procedure that meet programmed criteria for VTE will be submitted to the CEC for endpoint adjudication. In addition to confirmation of VTE, the events will be evaluated by the CEC for clinical significance. Details on endpoint definitions, adjudication criteria, and all other CEC processes/procedures are detailed in the CEC charter.

Postoperative Mortality or AEs Resulting in Death

All deaths (including AEs resulting in death) that occur within 30 days of the study procedure will be adjudicated by the CEC for endpoint criteria. This includes assessment of the timing and nature of the mortality (cardiac vs. non-cardiac death). *For the purposes of this study, fatal bleeding will be considered a type of cardiac death.* Details on endpoint definitions, adjudication criteria, and all other CEC processes/procedures are detailed in the CEC charter.

Safety Reporting to the FDA

The Sponsor will provide safety reports (of adverse events, including relatedness to the device, severity, outcome/resolution, and all deaths) to the FDA for each set of 20 subjects enrolled. These reports are independent of the required annual reports for all IDEs.

The Sponsor will perform ongoing safety evaluations of any deaths as they occur in the study and share the information with the agency as requested. Specifically, if four or more of the 20 study subjects within each reporting set die within 72 hours of the device therapy, the Sponsor will send an immediate report of those deaths to the FDA for review.

9.2.2. Medical History

Medical history will be obtained at Screening and should include demographic information (date of birth, biologic sex, race, ethnicity) and subject's medical and surgical history. The medical history must be documented in the subject's eCRF.

9.2.3. Clinical Laboratory Evaluations

Blood samples will be collected and documented by the Investigator (or designee) for all clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 4. Local clinical laboratory assessments (including clinical chemistry, hematology, and coagulation tests) are listed in Appendix 2. The handling and management of these samples will be per institutional protocols. **Of note:** if multiple sets of labs are obtained for a subject within the same post-operative day (either as part of standard institutional protocols, or due to changes in the subject's clinical picture), the lab assessments obtained at the time which *most closely approximates* those listed in **Table 6: Schedule of Assessments** should be the values entered into the EDC for study purposes.

Instructions for the collection and storage of study samples that will be analyzed by the Central Laboratory are provided in the Study Laboratory Manual.

9.2.4. Vital Signs

Supine blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 4. Vital signs may also be performed at other times if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

9.2.5. Physical Examination

Body mass index will be calculated using the subject's body weight and height at the time of screening and documented with other demographic information (Schedule of Assessments, Appendix 4). A physical exam will be performed and documented at the time of screening/subject enrollment. Physical exams performed as part of standard of care on the day of screening but occurring prior to signing of informed consent may be documented as the screening PE. A physical exam will be repeated on the day of the procedure if the day of the procedure is different than the day of screening.

9.2.6. Other Assessments: Blood Products and Blood Loss

Intraoperative and postoperative blood loss and chest drainage volumes (chest drainage includes output from all chest and mediastinal tubes) will be measured and documented at the times indicated in the Schedule of Assessments in Appendix 4. Cell Saver will ***not*** be included in the calculation of blood product transfusions, as this is volume that would normally be given back as part of standard of care. Chest tube drainage will be recorded in the corresponding *Chest Tube Drainage eCRF* for at least 24hrs post-operation, unless unable to do so (i.e., subject death prior to 24hrs). Volume of blood loss not coming from chest/mediastinal drainage will be documented separately, in the corresponding *Blood Loss (Non-Chest Drainage) eCRF* where applicable. Blood products received by the subject will be recorded in the corresponding *Transfusion eCRF*.

9.3. Blood Sampling for Drug Removal

Blood samples for the analysis of plasma apixaban and rivaroxaban concentrations will be collected at the times indicated in the Schedule of Assessments in Appendix 4 and will be stored until analysis. A pre-CPB sample will be obtained prior to the start of CPB and may be performed up to 2 hours prior to skin incision. While the subject is on CPB, serial samples will be drawn at 30-minute intervals following initiation of CPB, through the first 2 hours of CPB. Sampling times will be at 30 (±15) minutes, 60 (±15) minutes, at 90 (±15) minutes, and at 120 (±15) minutes of CPB time. A post-CPB sample will be obtained *as soon as possible following the end of CPB,* and *no later than 30min* after the subject has been disconnected from the CPB circuit.

If the total CPB time required for the procedure is <120min (2hrs), the serial sampling will only be performed through the required duration of CPB. For procedures requiring >120min (2hrs) of CPB time, serial sampling will ***not*** extend beyond this time point, as the incremental change is expected to be minimal compared to the post-CPB value. Processing, storage, and shipping instructions for these blood samples will be provided by the Sponsor (or designee) to the investigation sites and detailed in the Study Laboratory Manual. Samples will be stored and analyzed at a designated bioanalytical laboratory using a validated assay. Any residual samples will be destroyed at the completion of the final investigation report or if the subject withdraws assent/consent to use the sample for the research purposes of the investigation.

10. CONCOMITANT MEDICATIONS

Medication history and concomitant medications will be recorded in the eCRF. The medication history will include all acute and chronic prescription and over-the-counter medications taken during the 30 days prior to Screening. Medication history will be repeated on the day of the procedure if different from the day of screening.

All medications administered during the Screening, Pre-CPB, Intraoperative, Post-CPB, and during the Postoperative Phases must be collected. Unless medically necessary, concomitant medications should be withheld two hours prior to and during therapy with the investigational device. This is to reduce risk of unintended removal and inadequate delivery of these medications.

Study subjects may, in addition to apixaban and rivaroxaban, also be receiving other antithrombotic medications during their current hospitalization that could contribute to bleeding. The use of antithrombotic medications will be reviewed during the screening period. Certain agents and the timing of administration could confound the results of the study and are therefore listed as prohibited medications (see Appendix 5 for details). Subjects on prohibited medications at the time of surgery cannot be randomized. Each antithrombotic medication is categorized as allowed or prohibited in the study, and the reason for this categorization is provided.

Prior and concomitant medications will be coded using the latest version of the WHO Drug Dictionary, based on Anatomical Therapeutic Chemical classification and Preferred Name.

There are no protocol-specified prohibited medications during the Postoperative phase of the study.

11. STATISTICAL CONSIDERATIONS

General statistical considerations: descriptive summaries will be presented using mean with standard deviation (SD), median, minimum and maximum for continuous variables and as count and percent of subjects for categorical variables. Inferential statistical tests will be two-sided and use alpha (α) of 0.05 as a critical value, unless noted otherwise. Statistical analysis will be carried out using SAS Version 9.4 or later and/or R software language.

11.1. Statistical Power and Sample Size Determination

Overall study sample size is designed to provide adequate power for the primary effectiveness endpoint, at both the interim and final analysis, the key secondary endpoints, and selected secondary endpoints.

As noted above (**Section 6.2**), to maintain the balance between sites in terms of numbers of subjects randomized, study sites will be capped at randomizing a maximum of 15% of the overall study sample (i.e., 18 subjects). For sites with a total enrollment consisting of only one type of DOAC drug as per chance, the randomization cap will be replaced by a maximum of 10% of the overall study sample

(i.e., 12 subjects).

The null hypothesis for the primary composite endpoint is represented by:

H_0: The distributions of the components are the same in the two treatment groups

The alternative hypothesis for the primary composite endpoint is represented by:

H_A: For at least one component, the distribution is different between the treatment groups

The null hypothesis for the first key secondary endpoint is represented by:

$$H_0: \pi_{DS} = \pi_{SOC}$$

The alternative hypothesis for the first key secondary endpoint is represented by:

$$H_A: \pi_{DS} \neq \pi_{SOC}$$

where $\pi_{1,DS}$ and $\pi_{1,SOC}$ are the pre-CPB vs. post-CPB mean percent changes in blood apixaban levels with DrugSorb-ATR (DS) and Control (SOC), respectively. The second key secondary endpoint null and alternative hypotheses take the same form as the first key secondary endpoint but substituting rivaroxaban for apixaban.

The null hypothesis for the first secondary endpoint is represented by:

$$H_0: \pi_{DS} = \pi_{SOC}$$

The alternative hypothesis for the first secondary endpoint is represented by:

$$H_A: \pi_{DS} \neq \pi_{SOC}$$

where π_{DS} and π_{SOC} are the mean 24-hour CTD volumes with DrugSorb-ATR (DS) and Control (SOC), respectively. The following additional secondary endpoints, for which power is formally allocated (see below), take the same form of null and alternative hypotheses as above: platelet transfusions (mean number of units) and pRBC transfusions (mean number of units).

Approximately 120 combined DOAC subjects meeting the study inclusion criteria (**Section 4.4.1**) will be randomized in a 1:1 ratio to the treatment and control arms. A combined DOAC population is planned for analysis in the current study since apixaban and rivaroxaban share the same mechanism of action, same indications for use, same risk for post-surgical bleeding outcomes, have been shown in *ex vivo* testing to have nearly identical removal rates when treated with the study device, and are therefore considered exchangeable.

In terms of the composite primary effectiveness bleeding endpoint, while bleeding is known to be of significant risk in patients on both apixaban and rivaroxaban undergoing CT surgery without preoperative washout, literature quantifying postoperative bleeding outcomes is limited in this specific population. However, published real-world use experience from the Asklepios Klinik St. Georg research group (Hamburg, Germany) has demonstrated highly similar treatment effects for intraoperative CytoSorb® removal of ticagrelor and rivaroxaban in patients undergoing emergent CT surgery. [12] The difference between treatment and control groups regarding postoperative blood loss (in the form of 24hr chest tube drainage volume), reoperation rates for bleeding, and transfusion volumes were comparable between the ticagrelor and rivaroxaban cohorts. Thus, for the purpose of this study, we will anticipate the same treatment effects for DrugSorb-ATR therapy in subjects

undergoing CT surgery (within 36 hours of last DOAC dose) as were utilized for the STAR-T trial (which enrolled subjects undergoing CT surgery within 48 hours of last ticagrelor dose). The difference in timing between last drug dose and start of surgery for the DOAC vs. ticagrelor studies is necessary due to the difference in recommended washout periods between the DOACs and ticagrelor.

Because of exchangeability between apixaban and rivaroxaban, the anticipated proportions of individual DOACs expected in the trial (ranging from 40% - 60%, reflective of real-world use patterns), are not assumed to impact power or sample size. Assuming a 5% dropout rate, a total of 114 subjects (57 per arm) are expected to be evaluable for effectiveness and safety. Sample size is based on published response rates for the primary effectiveness Win Ratio sub-components, as noted for rivaroxaban and ticagrelor (above) with a bridge to apixaban, and can be calculated via an iterative simulation process with programming code available in an appendix to Redfors et al. (2019). [16] As a sensitivity exercise, power was estimated under varying conditions where the ratios of apixaban to rivaroxaban subjects were allowed to range from 40% to 60%, for either drug, and under assumptions of +/-5% worse vs. better outcomes for apixaban as compared to rivaroxaban (see **Table 3**). Power for the study to reject a false null hypothesis is formally estimated where apixaban is assumed equally comparable to rivaroxaban, at a subject ratio of 50:50 (see **bold** results in **Table 3**, below).

Table 3. Win Ratio Effect Size Assumptions with Power and Sample Size Estimates Under Varying Conditions

A:R* Com-para-bility	Ratio A:R	n Per Group	Effect Size						Power
			Component #1		Component #2		Component #3		
			Fatal Bleeding		UDPB (Class ≥2)		24hr CTD		
			Treatment Event	Control Event	Treatment Event	Control Event	Treatment Mean (SD)	Control Mean (SD)	
A Has 5% Higher Event Rate Than R Among Treated Subjects	40:60	Interim Analysis N=39	3.06%	3.00%	24.79%	40.50%	489.6 (253)	800 (253)	88.1%
	40:60	End of study N=56	3.06%	3.00%	24.79%	40.50%	489.6 (253)	800 (253)	99.3%
	50:50	Interim Analysis N=39	3.07%	3.00%	24.91%	40.50%	492.0 (253)	800 (253)	87.1%
	50:50	End of study N=56	3.07%	3.00%	24.91%	40.50%	492.0 (253)	800 (253)	99.2%
	60:40	Interim Analysis N=39	3.09%	3.00%	25.03%	40.50%	494.4 (253)	800 (253)	86.0%
	60:40	End of study N=56	3.09%	3.00%	25.03%	40.50%	494.4 (253)	800 (253)	99.2%
A = R Event Rate Among Treated Subjects	40:60	Interim Analysis N=39	3.00%	3.00%	24.30%	40.50%	480 (253)	800 (253)	91.3%
	40:60	End of study N=56	3.00%	3.00%	24.30%	40.50%	480 (253)	800 (253)	99.5%
	50:50	**Interim Analysis N=39**	**3.00%**	**3.00%**	**24.30%**	**40.50%**	**480 (253)**	**800 (253)**	**91.3%**
	50:50	**End of study N=56**	**3.00%**	**3.00%**	**24.30%**	**40.50%**	**480 (253)**	**800 (253)**	**99.5%**
	60:40	Interim Analysis N=39	3.00%	3.00%	24.30%	40.50%	480 (253)	800 (253)	91.3%
	60:40	End of study N=56	3.00%	3.00%	24.30%	40.50%	480 (253)	800 (253)	99.5%
A Has 5% Lower Event Rate Than R Among Treated Subjects	40:60	Interim Analysis N=39	2.94%	3.00%	23.81%	40.50%	470.4 (253)	800 (253)	93.6%
	40:60	End of study N=56	2.94%	3.00%	23.81%	40.50%	470.4 (253)	800 (253)	99.7%
	50:50	Interim Analysis N=39	2.93%	3.00%	23.69%	40.50%	468.0 (253)	800 (253)	94.2%
	50:50	End of study N=56	2.93%	3.00%	23.69%	40.50%	468.0 (253)	800 (253)	99.7%
	60:40	Interim Analysis N=39	2.91%	3.00%	23.57%	40.50%	456.6 (253)	800 (253)	94.7%
	60:40	End of study N=56	2.91%	3.00%	23.57%	40.50%	456.6 (253)	800 (253)	99.8%

* A, R = apixaban, rivaroxaban.
Notes: n = number; UDPB = Universal Definition of Perioperative Bleeding; CTD = chest tube drainage (volume [mL]).
Component #1 minimum rates of 3.0% assumed as a conservative approach.
Component #2 rates based on Russo et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm. [42]
Component #3 rates based on Hassan et al. (2019), however, with a discount applied to bring the Treatment arm up to ~40% reduction on the Control arm. [12]

Using a Finkelstein – Schoenfeld test, a total of 57 subjects per arm ensures power of >99.2% for the primary effectiveness endpoint at the final analysis, using a two-sided alpha (α) of 0.05, and assuming an interim analysis for efficacy at 70% completion. [15] Power for each of the key secondary endpoints is estimated at 96.3% assuming a 40% ± 40% mean difference between treatment and control, where N=29 subjects receiving apixaban with N=29 corresponding controls along with parallel numbers of subjects receive rivaroxaban and corresponding control, based on a two-sample t-test assuming equal variance and a two-sided alpha of 0.05. For the 24-hour CTD secondary endpoint, assuming a treatment arm volume of 480 ± 253 mL and control arm volume of 800 ± 253 mL [12] [a discount is applied (see **Table 3** for details) to bring the Active arm up to ~40% reduction on the Control arm], power is similarly estimated at >99.9%. Power for comparisons of platelet transfusions between the treatment arm (0.32 ± 0.9 units) and control arm (1.6 ± 2.2 units) [43] is estimated at 98.0%, based on a two-sample t-test assuming unequal variance and a two-sided alpha of 0.05. Similarly, power for PRBC transfusions between the treatment arm (1.3 ± 2.1 units) and control arm (4.4 ± 5.7) [43] is estimated at 96.7%. Sample size and power for all secondary endpoints were calculated using PASS 2021 (NCSS, LLC. Kaysville, UT, USA, ncss.com/software/pass).

11.2. Analysis Populations

Enrolled subjects include all subjects who provide informed assent/consent. Enrolled subjects who do not meet criteria for study eligibility are deemed screening failures and will exit the study.

The **Intent-to-Treat (ITT)** Population will include all enrolled (assented/consented) subjects who are randomized.

The **modified Intent-to-Treat (mITT)** Population will include all randomized subjects who undergo the index surgical procedure **and** receive a study device (whether DrugSorb-ATR or *sham*). The main primary analyses of the trial will be performed in the mITT Population.

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the ITT and mITT populations. So long as the ITT and mITT populations are not identical, the ITT subjects who do not fall within the mITT population will be presented in a listing, including the reasons for why they did not receive a study device.

The **Per Protocol (PP)** Population will include all mITT subjects who have no major protocol violations. Analysis of the primary efficacy endpoint will be performed in the PP population as a sensitivity analysis.

The **Safety Analysis (SA)** Population will include all enrolled subjects who are treated or attempted treatment with a study device. “Attempted treatment” refers to any subject(s) who initiate treatment with a study device (whether DrugSorb-ATR or *sham*) during the index procedure but experience early discontinuation of treatment due to device deficiency, clinical judgement on the part of the investigator, adverse event, or other rationale. All safety analyses will be performed in the Safety Analysis population.

11.3. Effectiveness Analysis

The primary effectiveness endpoint will be evaluated using the Win Ratio method of analysis for a

hierarchical composite endpoint based on the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999; Pocock, et al., 2012) with three components ranked in order of clinical importance: a) fatal bleeding events occurring within 48hrs post-index procedure, b) moderate, severe, or massive perioperative bleeding events according to the Universal Definition of Perioperative Bleeding in Cardiac Surgery (UDPB) classification ≥2, and c) 24-hour chest tube drainage (mL) following surgery. [14] [15] The Win Ratio assigns "wins", losses", or "ties" in sequential comparisons between treatment and control arm subjects according to the hierarchical order of the components of the primary composite endpoint.

There are two key advantages to the Win Ratio method of analysis. First, the hierarchical assessment of the individual components of the composite endpoint according to their clinical significance. Second, the opportunity for different types of components, such as categorical versus continuous, to all be included thereby capturing all available information from each component to increase statistical power.[15] A Win Ratio along with a two-sided 95% CI will be estimated, and a Win Ratio greater than 1.0 favors the treatment arm; when the lower bound of a two-sided 95% confidence interval (CI) around the ratio exceeds 1.0, the treatment is shown to be statistically superior to control at alpha = 0.05.[16] The primary effectiveness analysis will use a combined DOAC population to evaluate the difference between the SOC (control) arm and the DrugSorb-ATR (investigational) arm.
The key secondary effectiveness endpoints are drug removal endpoints, namely the percent change in pre-CBP vs. post-CPB apixaban and rivaroxaban levels as measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS). Blood samples for drug removal analyses will be collected and analyzed by a central core laboratory.

Change from baseline in blood concentration of apixaban or rivaroxaban is defined as:

$$\frac{\text{pre-CPB [apixaban]blood - post-CPB [apixaban]blood *100\%}}{\text{pre-CPB [apixaban]blood}}$$

and

$$\frac{\text{pre-CPB [rivaroxaban]blood - post-CPB [rivaroxaban]blood *100\%}}{\text{pre-CPB [rivaroxaban]blood}}$$

Benchtop studies of drug removal by DrugSorb-ATR (data on file, CytoSorbents Corporation) demonstrate concentration and time dependent absolute drug removal, which are nearly identical for both apixaban and rivaroxaban. Based on these benchtop studies, a conservative estimate of 40% reduction in blood concentration of DOAC between pre- and post- DrugSorb-ATR removal is expected, with a standard deviation of 40%, in the treatment arm. Minimal change is expected in the control arm. A two-sample t-test will be used to evaluate the difference between treatment arms. Due to highly variable baseline drug levels in the study population, percent change from baseline will be analyzed as opposed to observed values.

Additional secondary endpoints include 24-hour CTD (volume [mL]), total platelet transfusions during the index hospitalization (volume [mL] and units), and total PRBC transfusions during the index hospitalization (volume [mL] and units). Twenty-four-hour CTD (mL) will be assessed via two-sample t-test for mean difference. In the event the assumptions for a two-sample t-test are not met, a nonparametric test such as a Mann-Whitney test will be employed, with median and range values provided in the output. An additional analysis of 24-hour CTD will compare the frequency of subjects falling into volume categories (i.e., <500 mL, 500 to <750 mL, 750 to <1000 mL, 1000 to <1250 mL, 1250 to <1500 mL, and ≥1500 mL), and will use a Fisher-Freeman-Halton exact test to compare treatment groups. The transfusion endpoints will all be analyzed using two-sample t-tests for mean differences, and Fisher-Freeman-Halton exact tests for units. In the event the assumptions for a two-sample t-test are not met, a nonparametric test such as a Mann-Whitney test will be employed, with

median and range values provided in the output. The remaining Win Ratio component parts will also be included as secondary endpoints: proportions of fatal perioperative bleeding events will be assessed via Fisher's exact test; and proportions of UDPB events (by category) will be assessed via a Fisher-Freeman-Halton exact test. All surgical re-exploration for excessive bleeding, including those events occurring beyond the timeframe captured within the UDPB component of the primary endpoint will be captured as a secondary endpoint. Time to re-exploration will be considered.

Type I error (alpha, α) will be preserved from inflation due to multiplicity across the primary effectiveness, key secondary, and secondary endpoints via a hierarchical closed testing step-down approach. Only if preceding endpoints are declared statistically significant at the alpha 0.05 level, can further endpoints also be declared significant. The order of hierarchical testing will follow the order of primary, key secondary, and secondary endpoints as listed in the paragraph above, namely: the primary endpoint will be tested first, followed by the first key secondary endpoint (percent change in pre-CPB vs. post-CPB blood apixaban levels), followed by the second key secondary endpoint (percent change in pre-CPB vs. post-CPB blood rivaroxaban levels), followed by the first secondary endpoint (24-hour CTD), second secondary endpoint (platelet transfusions), and lastly the third secondary endpoint (pRBC transfusions).

11.4. Subgroup Analysis

Results comparing the two treatment arms based on the components of primary effectiveness endpoints will be contrasted across clinically meaningful subgroups according to the following factors:

- DOAC type (apixaban vs. rivaroxaban),
- Planned surgery type (CABG-alone vs. all other types of CT surgery)
- EuroScore II score (<7% vs. ≥7%),
- STS Risk score (<4% [low], 4-8% [intermediate], ≥8% [high]),
- Left ventricular ejection fraction (LVEF) [≥50% (normal), 40-49% (mild dysfunction), 30-39% (moderate dysfunction), <30% (severe dysfunction)]
- Baseline thrombocytopenia (platelet count <150,000 μ/L vs. ≥150,000 μ/L),
- Age group (<65 vs ≥65 years old),
- Biologic sex (F vs. M),
- History of MI (Y vs. N), and
- History of stroke (Y vs. N).

For the fatal bleeding events occurring within 48hrs post-index operation, and moderate, severe, or massive bleeding events components, a logistic regression will be utilized with treatment, group and their interaction included in the model. Details will be provided in the SAP.

11.5. Exploratory endpoints

Other exploratory endpoints include:

- Area under the concentration time curve (AUC), using the trapezoidal approach, for intraoperative apixaban or rivaroxaban pharmacokinetic (PK) concentration
- Operative time (measured from start of skin incision to completion of chest closure)
- Duration of ICU stay
- Duration of hospital stay
- 30-day hospital re-admissions

Details on methods of analysis for exploratory endpoints will be provided in the SAP.

11.6. Interim Analysis

An interim analysis with unblinded efficacy assessment is planned once 70% of evaluable subjects (n=40 per group) have completed the primary effectiveness assessment, including follow-up period. All data for the interim primary effectiveness endpoint will be fully adjudicated by the CEC prior to analysis. The interim evaluation will be performed with possible early stopping for efficacy on the basis of a Lan-DeMets O'Brian-Fleming spending function, which generates group-sequential boundaries that resemble O'Brian-Fleming boundaries, with experiment-wise error preserved at 0.05. [44, 45] Based on simulation results, a Win Ratio Z-value boundary of 2.44 would need to be crossed, corresponding to a two-sided p-value of 0.0148. Should the interim efficacy boundary not be crossed, a total alpha of 0.0148 would be spent at the interim, plus 0.0352 spent at the final analysis. In this case, at the final analysis a Win Ratio Z-value of 2.00 would need to be crossed, corresponding to a p-value of 0.0456, to declare a statistically significant Win Ratio result favoring the treatment arm. The estimated probability of stopping due to efficacy at the interim is >88.1%.

To maintain study blinding, the interim analysis will be conducted by an independent unblinded statistician separate from the day-to-day operational team with appropriate experience. Enrollment will not be paused during the interim analysis. Interim analysis results will be shared only with the DSMB, which will make a decision to either stop the study early due to overwhelming efficacy or continue until the final analysis. The FDA will be immediately notified of any decision by the DSMB to halt or terminate the study early. Should the study stop early, a final analysis will also take place that will include any additional subjects who were treated and followed-up during the conduct of the interim analysis.

To prevent potential operational bias resulting from the interim analysis, the clinical personnel at sites may not be informed of the interim results. Details on the interim analysis methodology will be provided in the SAP.

11.7. Treatment of Missing Data

Every effort will be taken to obtain data entry compliance of all critical fields during the study. The study assumes 5% of the primary effectiveness and safety data will be missing. Reasons for missing data will be collected and a distribution of the prognostic factors in subjects with and without missing data will be compared to identify any confounding factors. Sensitivity analyses will be conducted to assess the sensitivity of the results to assumptions underlying the missingness mechanism. Details will be provided in the SAP.

11.8. Safety Analysis

The incidence of all AEs occurring after the start of the CPB procedure will be summarized by treatment group using frequency and percentage. AEs that occur following informed consent but prior to the start of CPB will not be included in this safety analysis but will be provided in a listing. Within the Safety Analysis, AEs will be summarized by severity and relationship to the study device as determined by the Investigator (or designee). Discontinuations due to AEs, and SAEs will be summarized. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) according to system organ class and preferred term, prior to database lock.

Observed values for clinical laboratory test data and vital signs, along with change from baseline results, will be summarized by collection time point. A summary of clinically notable values will be provided.

Safety results will be further analyzed by clinically meaningful subgroups according to the following risk stratification criteria: age group, gender, history of prior MI, prior stroke, prior hypertension, prior hyperlipidemia, prior diabetes, and prior tobacco use. Details will be provided in the SAP.

Listings will be provided of all safety endpoint data.

Further details regarding presentation and analysis of safety data will be detailed in the SAP.

11.9. Device Malfunctions/Deficiencies

A summary of device malfunctions/deficiencies will be provided by treatment arm. All malfunctions/deficiencies will be listed.

11.10. Disposition and Baseline Characteristics

Number and percentage of subjects discontinuing prematurely from the study will be provided by treatment group and by reason discontinued. All data for background and demographic variables will be summarized and listed by treatment group and subject. Relevant medical history, current medical conditions, and incidence of prior and concomitant medications will be summarized by treatment group as well as listed.

12. DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), the sponsor's designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

12.1. Data Management Procedures

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during the course of the study, which are part of a database that meets 21 CFR Part 11 requirements. eCRFs must be fully completed for each subject and electronically signed by the Investigator when complete.

Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study subject's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study Investigator, study name, subject number assigned and a statement that consent was obtained.
- Dated and signed notes from each study subject visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).

- Information related to adverse event(s).
- Study subject's condition upon completion of or withdrawal from the study.
- Discharge summaries/procedure reports.

12.2. Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), investigation-related forms, investigation reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the clinical investigation plan (CIP), investigation report, or investigation data are included in a public registry, all identifiable information from individual subjects or Investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal investigation-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her investigation-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

12.3. Data retention

Maintenance of study records should be obtained for a period of five (5) years after the latter of two occurrences:

1. The date when the investigation is terminated or completed, or
2. The date that the records are no longer needed to support a regulatory approval.

These documents should be retained for a longer period, however if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12.4. Investigator Records

Investigators will maintain complete, accurate, and current study records. Investigator records shall include the following materials:

- **Correspondence:** All significant correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
- **Subject Records:** Signed Informed Consent Forms, copies of supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50).
- **Clinical Investigational Plan/Protocol:** A current copy of the Clinical Study Protocol and amendments including Instructions for Use of the DrugSorb-ATR device and copies of the eCRFs.
- **Institutional Review Board (IRB) Information:** All information pertaining to IRB review and approval of this clinical study including a copy of the IRB letter approving the clinical study, a blank Informed Consent Form approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, part 56), and that the IRB approved the clinical study protocol.
- **Investigator Agreements:** Copies of the signed Investigator, Sub-Investigator Agreements

with accompanying curriculum vitae. Signed Protocol pages.

- **Study Documents:** Including Investigational Device Accountability logs (including device shipment list/packing lists), Screening and Enrollment logs, and Site Visit logs
- **Other:** Any other records that may be required by applicable state or federal laws.

12.5. Investigator Reports

The Investigator will prepare and submit the designated reports listed in **Table 4**.

Table 4. Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by the Investigator for:	Time of Notification/Report Completion
Enrollment Notification eCRF	Sponsor	Within 24 hours of the subject signing the ICF
SAE/SADE/UADE eCRF	Sponsor	Within 24 hours of knowledge or as required by the IRB
All other eCRFs	Sponsor and IRB (as required)	Within 10 business days (or as required by IRB for AE eCRFs)
Device deficiency or device observation eCRF	Sponsor	Within 24 hours of knowledge
Subject Death or withdrawal	Sponsor and IRB (as required)	Within 24 hours of knowledge
Withdrawal of IRB or FDA Approval	Sponsor	Within 24 hours of knowledge
Informed Consent Not Obtained	Sponsor and IRB	Within 24 hours of knowledge or as required by IRB
Progress report	Sponsor and IRB	Annually
Final summary report	Sponsor, IRB, and FDA	Within six months of study completion
Other reports	Sponsor and IRB and FDA	As needed

13. QUALITY CONTROL AND ASSURANCE

13.1. Site and Investigator Selection

The Sponsor selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. The investigational sites will be selected using combined current assessments of site and investigator qualifications.

13.2. Protocol Deviations

An Investigator is not allowed to deviate from the Protocol without the prior written approval of the Sponsor. Under emergency circumstances, deviations from the Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB (as required) as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in the protocol, visits performed outside of the protocol specified visit window, and missed study visits. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, Good Clinical Practices, and any conditions of approval imposed by their IRB.

All deviations are reviewed and assessed for their impact on subject safety by the Sponsor or designee. The PI and study staff are responsible for knowing and adhering to their IRB reporting requirements.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to obtain subject's informed consent prior to any study-related activities;
- Failure to conduct protocol required clinical follow-ups;
- Failure to conduct protocol required clinical follow-ups within time windows; and,
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Subjects enrolled at these sites will continue to be followed per the clinical protocol.

13.3. Protocol Deviation Process

Investigators must report protocol deviations to the Sponsor within 10 working days of investigational site knowledge of the deviation by entering data into the protocol deviation log. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported within 24 hours to the Sponsor and IRB if required by the IRB.

13.4. Corrective/Preventative Action

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons:

- Repeated failure to complete Electronic Case Report Forms (eCRFs);
- Failure to obtain Informed Consent;
- Failure to report Serious Adverse Events within 24 hours of knowledge;
- Loss of or unaccountable investigational device inventory;
- Repeated protocol violations;
- Failure to enroll an adequate number of subjects

13.5. Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the investigation will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit investigation-related monitoring, audits, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this investigation including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented.
- An Investigation Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the investigation is being conducted in accordance with the currently approved CIP and any other investigation agreements, ISO GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this investigation must be retained by the Investigator in the investigation site archive for at least 5 years after the end of the investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

14. TERMINATION OF STUDY OR STUDY SITE PARTICIPATION

The Sponsor may terminate the study at any time. Reasons for study termination may include but are not limited to any of the following:

- Adverse events unknown to date (i.e., not previously reported in any similar investigation or in market use with respect to their nature, severity, and/or duration).
- Increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs.
- Medical or ethical reasons affecting the continued performance of the investigation.
- Difficulties in the recruitment of subjects.
- Cancellation of device development.

If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All subjects already enrolled will continue to be followed for the planned course of study described in this protocol. The study will be terminated following the final follow-up visit of the last enrolled subject.

In addition to the corrective actions listed in **Section 13.4**, the Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum subject enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

15. ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1. Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and 21 CFR Part 812, 50, 54, 56. The clinical investigation shall not begin until the required approval from the IRB has been obtained, if appropriate. Any additional requirements imposed by the IRB, or regulatory authority shall be followed.

15.2. Institutional Review Board (IRB)

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB. Any major amendments to the protocol or consent materials must also be approved before they are placed into use.

15.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout an individual's study participation. Discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study product.

Consent may be provided by: 1) individual subject providing informed consent; 2) assent of a guardian, healthcare proxy, or welfare attorney on behalf of a subject without capacity to consent (vulnerable or incapacitated individual). Details of the process for obtaining and documenting informed consent are provided in Appendix 3. Failure to obtain informed consent prior to initiation of study treatments will need to be documented as a protocol deviation and be reported in accordance with regulations.

15.4. Subject Confidentiality

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the Principal Investigator or institution shall obtain

permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

16. PROTOCOL AMENDMENTS

The Protocol, CRFs, ICF and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of the document. Proposed amendments to the Protocol shall be agreed upon between the Sponsor and Principal Investigator(s), or the coordinating investigator. The amendments to the Protocol and the subject's Informed Consent Form shall be notified to, or approved by, the IRB and regulatory authorities as required. For non-substantial changes (e.g., minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

17. PUBLICATION POLICY

CytoSorbents manages its clinical studies in an ethical and rigorously scientific manner, working with leading experts in the field, to clearly and publicly demonstrate the benefits, risks, and value of DrugSorb-ATR to caregivers and study subjects alike. The Sponsor accepts the obligation to facilitate publication of medically important clinical data in a timely, objective, accurate, and balanced manner, regardless of the outcome of this trial. To ensure that an accurate record of the study data is presented to the public, CytoSorbents understands the need to allow sufficient time for careful preparation, analysis, interpretation, and review of study data and reports prior to their dissemination.

Safety and Efficacy Data generated for all prespecified primary and secondary endpoints, shall be compiled, analyzed, reviewed, and published in the following manner:

- The Principal Investigator(s) and Sponsor shall compile and disseminate a clinical summary report that shall be disseminated to CytoSorbents (as Sponsor), all participating local and central IRBs, and the FDA. Data from this Summary Report shall also be published on the ClinicalTrials.Gov website simultaneously.
- Following database closure, a study publication shall be submitted to a peer reviewed journal within 18 months of database closure. In the event that the study is terminated early, a publication of this data will be submitted within 12 months of database closure.

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19. APPENDICES

Appendix 1: Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a subject regardless of relationship to the device or procedure. Throughout the study, the Investigator or designee will determine adverse event (AE) occurrences. All AEs that occur starting from subject enrollment through follow-up will be reported. As a matter of semantics, AEs that are new onset or worsen in severity ***after the start of the cardiopulmonary bypass procedure*** are considered Treatment-emergent AEs. This term does ***not*** include adverse events occurring *prior* to the start of CPB but *after* the signing of the ICF (assent or consent). As previously discussed in **Section 11.6**, only the treatment-emergent AEs will be included in the safety analysis. This will be further detailed in the SAP.

Each adverse event is considered to be either anticipated or unanticipated as described below. The site is required to report the classes of adverse events that occur in the study (AE, SAE, and UADE) as described further below.

Severity Assessment

The Investigator will assess each adverse event for severity in accordance with the following categories: mild, moderate, severe, life-threatening, or death.

The severity assessment is distinct from the seriousness assessment (see definition of SAE below).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that meets one or more of the following criteria:

- led to death;
- led to a life-threatening illness or injury;
- led to in-patient hospitalization or prolongation of existing hospitalization;
- led to disability or permanent damage to a body structure or body function;
- led to fetal distress, fetal death, congenital anomaly, or birth defect;
- required medical or surgical intervention to prevent permanent impairment or damage; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of Hospitalization
Adverse events requiring hospitalization or extended hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious. *Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health is not considered a serious adverse event.*

Serious AEs occurring after 30 days post-operation are to be reported to the Sponsor if, in the judgment of the Investigator, there is an association between the event and the previous use of the device under investigation.

Causality Assessment

The Investigator will assess each adverse event for relationship to the following (causality), and relationship classified as unrelated, unlikely related, possibly related, probably related, or definitely related:

> **Investigational Treatment/Device:** An investigational device/treatment-related adverse event is one which in the judgment of the Investigator, results as a consequence of the investigational device/treatment. Clinical judgement in conjunction with the relevant documents, such as the Investigator's Brochure and the Clinical Investigational Plan shall be applied in the determination of whether the AE might be related to the device/treatment. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall be considered.
>
> **Surgical Procedure:** The investigator will distinguish between the events potentially related to CPB and the investigational device from those related to the underlying surgical procedures. A procedure-related adverse event is one which, in the judgment of the Investigator, results as a consequence of the subject's surgical procedure and is not specific to the investigational device/treatment used or the associated CPB circuit. Complications occurring during a procedure are considered not related to the device if the complication would have been applied to the subjects in the absence of the investigational device use/application. Adverse events that have previously been determined to be related to the investigational device should not also be assessed as being related to the surgical procedure.

Causality assessment will also be performed during CEC adjudication of relevant events. Guidelines for CEC causality assessments are provided in the CEC charter.

Action Taken for Adverse Events

The Investigator or designee will record the action taken for the AE within the electronic Case Report Form (eCRF) in accordance with the following categories: treatment interrupted, treatment withdrawn, medication, procedure/intervention, transfusion, other/unknown, or none.

Outcome

The Investigator or designee will record the outcome of the AE within the electronic Case Report Form (eCRF) in accordance with the following categories: resolved without sequelae, resolved with sequelae, ongoing, or resulted in mortality.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing AE that is related to the investigational medical device at the 30-day Follow-up Evaluation will be followed up, where possible, until resolution or stabilization. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related to the investigational medical device at the 30-day Follow-up Evaluation can be closed out as ongoing at the Investigator's discretion.

Adverse Device Effect:

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or any malfunction of the investigational medical device. The definition also includes any event resulting from use error or from intentional misuse of the investigational medical

device. These events can be classified as either serious or not serious in accordance with the definition for SAEs above. Serious adverse device effects are also commonly referred to by the abbreviation SADE.

Unanticipated Adverse Device Effect:

An unanticipated adverse device effect (UADE) is any adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. These events can be classified as either serious or not serious in accordance with the definition for SAEs above. In the event of a possible UADE, the subject blind may be broken as per **Section 6.3.3** above. This will enable confirmation of relationship between the adverse event and device exposure and facilitate appropriate safety procedures as well as regulatory reporting per guidelines.

Anticipated Adverse Events/Device Related Adverse Events

A variety of complications are expected to occur in subjects undergoing CPB and cardiothoracic surgery, regardless of whether DrugSorb-ATR is used. These may include, but are not limited to:

Serious, but less common, risks:

- Bleeding during or after the surgery including bleeding in relation to anticoagulation
- Blood clots that can cause heart attack, stroke, or lung problems
- Heparin-induced thrombocytopenia
- Bypass induced thrombocytopenia
- Reduction in platelets
- Infection, including pneumonia
- Organ injury including:
    - Respiratory damage causing breathing problems or failure to wean from the ventilator
    - Cardiac dysrhythmias/arrhythmias
    - Kidney injury or renal failure
    - Cognitive impairment
- Death

Less serious, but more common risks and adverse events:

- Low-blood pressure
- Nausea and/or vomiting
- Hypothermia and/or Chills
- Allergic response to device materials
- Reduction in platelet count
- Reduction in white blood cell count
- Reduction in proteins (albumin, total protein)
- Coagulation within device
- Heparin-induced thrombocytopenia

Potential Adverse Device Events Directly Related to DrugSorb-ATR:

- Removal of drugs and hormones
- Allergic response to device materials
- Reduction in platelet count
- Reduction in white blood cell count
- Reduction in proteins (albumin, total protein) which may increase with CPB duration.
- Reductions in serum calcium (as a consequence of reductions in albumin)
- Coagulation within device
- Infection
- Blood loss
- Hemolysis
- Device leakage
- Circuit leakage
- Death

Investigator Reporting:

The Investigator at each participating center is ultimately responsible for reporting adverse events to the Sponsor or its designee. The information to be reported on the adverse event should include the start date of the adverse event, treatment, resolution, and assessment of both the seriousness and the relationship to the investigational device. The Investigator (or designee) is required to complete the adverse event eCRF at each study visit if an adverse event occurs. One adverse event eCRF must be completed for each adverse event. The timing of mandatory Investigator reports is provided in **Table 4**.

If there is a device malfunction or other observation, the Device Observation CRF requires the Investigator to indicate if the observation resulted in an adverse event and indicate if complications are related to the device, procedure or underlying disease.

Sponsor Reporting:

Reports will be provided to the FDA as required under §812.150. The details will be provided in the Study Reference Manual for the trial.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:
Alanine aminotransferase [a] Albumin [a] Alkaline phosphatase [a] Aspartate aminotransferase [a] Blood urea nitrogen Calcium Ionized Calcium [a] Chloride Creatinine Direct bilirubin [a] Gamma-glutamyl transferase [a] Glucose Potassium Sodium Total bilirubin [a] Total protein [a]	Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell (WBC) count Differential [a]
Coagulation tests:	**Other, including cardiac biomarkers**
Coagulation Panel: Activated partial thromboplastin time International normalized ratio Prothrombin time Fibrinogen [a] **Point of Care Test(s):** Activated clotting time (ACT) [*refer to Schedule of Assessments for specific timing of sampling*]	Serum pregnancy test[b] Cardiac troponin (cTn)[c]

[a] Performed only if part of routine standard of care. Sponsor agrees to forego the data if the assessments are not performed and recorded
[b] Performed in serum at Screening for all females of childbearing potential. Pre-consent test results done during the current admission MAY be used. Pre-consent test results done before the current admission MAY NOT be used.
[c] Performed in serum Screening for all females of child-bearing potential. Post-op testing will be per institutional standard of care, or as indicated by symptoms and concern for perioperative myocardial infarction

Appendix 3: Regulatory and Ethical Considerations

This investigation will be conducted in accordance with the Clinical Investigation Plan (CIP) and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and 21 CFR Part 812, 50, 54, 56.
- Applicable International Organization for Standardization (ISO) ISO14155 Clinical investigation of medical devices for human subjects — Good clinical practice, Good Clinical Practice (GCP) Guidelines.

The CIP, CIP amendments, Informed Consent Form (ICF) along with associated information sheets, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC and regulatory authority before the investigation is initiated.

Any substantial CIP amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC, IRB, and regulatory authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to investigation subjects or any non-substantial changes, as defined by regulatory requirements.

Informed Consent for Non-vulnerable Populations

Subjects will be given an opportunity to ask questions about the investigation prior to providing consent for participation. Written documentation of informed consent is required prior to starting the intervention/administering the study product. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the signed Informed Consent Form will be given to the subject, and another will be maintained in the subject's records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

When informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the legally authorized representative, if present, shall be requested (see the below section on ***Informed Consent for Vulnerable Populations***).

If informed consent is not obtained prior to any research procedures being conducted, the investigative site must notify the Sponsor and IRB within 24 hours of knowledge of the incident.

If new information becomes available, that can significantly affect a subject's future health and medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continued informed consent in writing.

Informed Consent for Vulnerable Populations

Considering the nature of the clinical investigation as well as the clinical investigation population, is it likely that potential subjects may not be able to give voluntary written informed consent in advance of the procedure (vulnerable individual lacking capacity). A personal legally authorized representative (preferably the nearest relative or healthcare proxy) of the subject shall be consulted in the event the subject is unable to consent for themselves and this person will be the one responsible for assenting to

the subject participation in the clinical investigation. After the procedure is completed, the consent of the subject will be obtained as soon as the subject has recovered capacity. Upon regaining capacity, those subjects who do not wish to consent, may request that all data obtained under the assent be withdrawn from the study database.

Informed Consent for Subjects Unable to Read or Write

Informed consent shall be obtained through a supervised oral process if the subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written Informed Consent Form and any other information shall be read aloud and explained to the prospective subject and his/her legally authorized representative and, whenever possible, shall sign and personally date the Informed Consent Form. The witness also signs and personally dates the Informed Consent Form attesting that the information was accurately explained, and that informed consent was freely given.

Disclosure

All information provided regarding the investigation, as well as all information collected and/or documented during the course of the investigation, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Appendix 4: Study Schedules

Table 5. Schedule of Antithrombotic and Anticoagulation Management

Time period	Screening/ preoperative period	Operation	Postoperative day 1	>1-day post-operation	30-day follow-up
Subjects with ACS or coronary stent placement within the previous 6 months					
Aspirin	X	X	X[a]	X	X
$P2Y_{12}$ inhibitor	Prohibited	Prohibited	SOC ---------- SOC		
Apixaban or rivaroxaban	X[b]		X[c]	X[c]	X[c]
Thromboprophylaxis		SOC ---------- SOC			
All other subjects					
Aspirin	SOC ---------- SOC				
$P2Y_{12}$ inhibitor	Prohibited	Prohibited	SOC ---------- SOC		
Apixaban or rivaroxaban	X[b]		X[c]	X[c]	X[c]
Thromboprophylaxis		SOC ----------SOC			

[a] Subjects not previously on Aspirin in the preoperative setting should be initiated on Aspirin therapy at 6 hours post-op, per institutional protocols
[b] Last dose is within 36 hours of operation start as per the study inclusion criteria.
[c] Timing of apixaban and/or rivaroxaban resumption (or any other form of therapeutic anticoagulation) in the postoperative period is at the discretion of the treating physician. Known thrombotic risk must be weighed against anticipated bleeding risk when making this decision.
SOC = per institutional protocols

Table 6: Schedule of Assessments

Study Procedures	**Screening**	**Pre-CPB**	**Operation**	**Post-CPB**	**Post-Operation**						**Follow-up Visit/End of Study/Early Termination**
Timepoint	Up to 36 hours before Operation	Within 2 hours before start of operation (i.e., skin incision)	From chest incision to chest closure	Within 30min after end of CPB	ICU Admission	POD 1	POD 2	POD 3	POD 4	POD 5-29	POD30 + 5 days
Informed consent/authorization [a]	X										
Inclusion/exclusion criteria	X										
Demographic information	X										
EuroScore II	X										
STS Risk Score	X										
Last pre-operation dose of DOAC (date, time, and dosage)	X										
Medication history within 30 days of study enrollment	X [r]										
Physical exam, height, weight [b]	X [r]										
Planned surgical procedure [c]	X										
Drug removal blood sampling [d]		X	X	X							
Medical history	X										
Concomitant medications	X	X	X		X	X	X	X	X	X [s]	X
EKG [e]	X				SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	
Pregnancy test [f]	X										
Cardiac troponin (cTn) [g]	X				SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	SOC [t]	
Hematology [g]	X				X	X	X	X	X	X [u]	
Clinical chemistry [g]	X				X	X	X	X	X	X [u]	
Coagulation tests [g]	X				X	X	X	X	X	X [u]	
Vital signs [h]	X				SOC	X	X	X	X	X [s]	SOC
CPB duration [i]			X								
DrugSorb-ATR flow rate & flow duration [i]											
Surgical procedure type [j]			X								
Activated Clotting Time (ACT) [k]			X	X							
Arterial Blood Gas (ABG) [l]			X	X	X						

Study Procedures	Screening	Pre-CPB	Operation	Post-CPB	Post-Operation						Follow-up Visit/End of Study/Early Termination
Timepoint	Up to 36 hours before Operation	Within 2 hours before start of operation (i.e., skin incision)	From chest incision to chest closure	Within 30min after end of CPB	ICU Admission	POD 1	POD 2	POD 3	POD 4	POD 5-29	POD30 + 5 days
Blood products [m]	X----------X					X	X	X	X	X [s]	
Operation blood loss and drainage [m]			X								
Post-Operation chest tube drainage				X----------X							
Post-Op blood loss & bleeding [m]					X	X	X	X	X	X [s]	X
Daily assessment						X	X	X	X	X [s]	
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X
Ventilation and mechanical support [o]					X	X	X	X	X	X [s]	
FiO2 [p]					X	X	X	X	X	X [s]	
Vasopressor requirements [q]					X	X	X	X	X	X [s]	

Abbreviations: AE = adverse event; CPB = cardiopulmonary bypass; D = day; h = hour; eCRF = electronic case report form; ICF = Informed Consent Form; ICU = Intensive Care Unit; POD = post-operative day; SOC = standard of care.

[a] Authorization or informed consent must be obtained at Screening (see Appendix 3)

[b] Body mass index will be calculated from the subject's height and weight measurements obtained at Screening or from the values in the medical record in the current hospital admission.

[c] Pre-randomization stratification will be performed based on the ***planned*** surgical procedure; changes in the planned surgical procedure should be updated within the IxRS system whenever possible to avoid any unintended protocol deviation.

[d] Blood samples will be collected for the determination of plasma DOAC concentration at a designated bioanalytical laboratory using a validated assay. The pre-CPB blood sample will be drawn prior to the start of cardiopulmonary bypass and can be up to 2hrs prior to skin incision. The post-CPB blood sample will be drawn as soon as possible following the end of CPB, and no later than 30min after the subject has been disconnected from the CPB circuit. During the procedure, while the subject is on CPB, serial sampling will be obtained q30±15min up through 2hrs of CPB. If the procedure requires a CPB time of <2hrs, then sampling will be q30±15min only up through completion of the CPB.

[e] Baseline EKG is required on file within the subject's medical record pre-op but does not need to have been performed within 36hrs of surgery.

[f] In all females of childbearing potential. Performed in serum. Pre-consent test results done during the current admission MAY be used. Pre-consent test results done before the current admission MAY NOT be used.

[g] Refer to Appendix 2 for a list of evaluations in the hematology, clinical chemistry, cardiac biomarker, and coagulation tests. During Screening, if consented subjects enter the Operation Phase without post-consent evaluation of hematology, clinical chemistry, or coagulation tests to record, the last pre-consent laboratory values MAY be used. Intraoperative ACT is documented in the ACT log, and not recorded in the Coagulation Test eCRF.

[h] Vital signs include supine blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature.

[i] Duration of CPB = time from the start of CBP to end of CPB, which may differ from duration of operation. Flow rate and flow duration for the device will be recorded q30±5min while patient is on CPB; flow rates are not mandated while subject is on hypothermic circulatory arrest (HCA).

[j] Details regarding the surgical type will be recorded. Delayed sternal closure will be recorded. ***Re-exploration/re-thoracotomy will be recorded according to the same schedule as AEs and documented in the re-operation eCRF***.

[k] ACT will be obtained once at 30min into CPB ±15min, and once within 30min post-protamine administration (post-CPB)

[l] During the operation phase, arterial blood gas analysis will be obtained at the following time periods: within 30min pre-CPB, 30±15min into CPB, within 30min post-CPB, and upon admission to the ICU

[m] Blood product administration will be monitored and recorded from the point of consent through discharge. Cell Saver will ***not*** be included as blood product administration. Blood loss and bleeding events will be monitored and recorded through follow-up, and drainage will be monitored from chest closure to 12h post-op (for UDPB class) and continued from 12hr post-op through at least 24h post-operation. Measurement of drainage after 24h and through time of chest/mediastinal drain removal will be per SOC.

[n] All AEs will be recorded from point of authorization to participate in the study through the 30-day Follow-up. If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the investigation treatment may be discontinued if deemed clinically necessary. Follow-up evaluations of the subject are to be performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant. Serious AEs occurring after 30 days post-operation are to be reported to the Sponsor if, in the judgment of the Investigator, there is concern for potential association between the event and the use of the DrugSorb-ATR device.

[o] If subject is intubated/requires mechanical ventilatory support, the maximum ventilation and mechanical support requirements will be recorded for each day.

[p] Documented in the ABG eCRF; only required if the subject is intubated or on mechanical ventilatory support

[q] The maximum vasopressor dosage will be recorded each day.

[r] Physical exam performed on the day of screening as part of standard of care but occurring prior to signing of informed consent *may* be used for the screening PE. The physical exam and review of concomitant medication history will be repeated on the day of the procedure, if the day of the procedure is different than the day of screening

[s] Assessments completed daily ***through hospital discharge***.

[t] In the advent of any cardiac ischemic AEs, EKG (to assess for Q waves) and cTn ***must*** be obtained. EKG will be provided as source documentation for CEC adjudication. cTn will be documented within the laboratory eCRF for CEC event adjudication

[u] Through postoperative day 5 only.

Appendix 5: Antithrombotic Medications Allowed/Disallowed in the Preoperative Period

Aspirin – allowed

Ticagrelor – any use within 7 days disallowed (as may have confounding effects on bleeding)

Clopidogrel – any use within 7 days disallowed (as may have confounding effects on bleeding)

Prasugrel – any use within 7 days disallowed (as may have confounding effects on bleeding)

Cangrelor – any use within 4 hours of (or during) the index procedure is disallowed (as may have confounding effects on bleeding)

Argatroban – any use within 4 hours of (or during) the index procedure is disallowed

Bivalirudin – any use within 2 hours of (or during) the index procedure is disallowed

Heparin – allowed

Low molecular weight heparin (e.g., enoxaparin) and fondaparinux – allowed

Dabigatran and edoxaban – any use within 5 days is disallowed, as it may have confounding effects on bleeding

Warfarin – any use within 7 days disallowed (as may have confounding effects on bleeding)

Tirofiban – any use within 8 hours disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 4 hours)[1]

Eptifibatide – any use within 8 hours disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 4 hours)[1]

Abciximab – any use within 5 days disallowed as may have confounding effects on bleeding (restoration of platelet function normally occurs within approximately 72 hours)[1]

References (for this appendix only):

1. Schrör K, Weber AA. Comparative Pharmacology of GP IIb/IIIa Antagonists. *J Thromb Thrombolysis*. 15:71–80.