Active Clearance Technology® Improves Post Operative Atrial Fibrillation- The ACT POAF Trial

Study Protocol #: MP-33-2015-1901

Clinical Study Support:

ClearFlow, Inc.
1630 S. Sunkist St., Suite E
Anaheim, CA 92806
USA

Active Clearance Technology® Post Operative Atrial Fibrillation Trial - The ACT POAF Trial

1. ADMINISTRATIVE INFORMATION AND KEY ROLES:

1.1 ***Protocol Title:*** Active Clearance Technology® Improves Post-Operative Atrial Fibrillation - The ACT POAF Trial

1.2 ***Coordinating Principle Investigator:*** Dr Philippe Demers

1.3 ***Clinical Study Support:*** Clinical Study Support has been provided by ClearFlow, Inc 1630 South Sunkist St., Suite E, Anaheim California, 92806, USA

1.4 ***Monitor:*** Trained monitors will conduct periodic site monitoring visits. Purpose of the visits is to verify that data entered to the study database matches the source data. Monitors will coordinate visits with the site personnel

2. SYNOPSIS

2.1 ***Protocol Title:*** Active Clearance Technology® Improves Post Operative Atrial Fibrillation- The ACT POAF Trial

2.2 ***Protocol Number:*** MP-33-2015-1901

2.3 ***Sponsor:*** ClearFlow, Inc. has provided partial support for this trial

2.4 ***Objectives:***

1. To assess the effectiveness of the PleuraFlow® Active Clearance Technology® (ACT) in reducing the rate of postoperative atrial fibrillation (POAF) among post cardiac surgery patients

2. To evaluate the impact of ACT on retained blood syndrome (RBS) and other complications after cardiac surgery.

2.5 ***Study Design:***

This is a prospective, randomized, single blinded two-arms, single-center Post Market Clinical Follow-Up (PMCF) Study. The test arm consists of consecutively enrolled cardiac surgery patients receiving ≤ two (2) PleuraFlow® chest tubes with Active Clearance Technology® and ≤ two (2) other commercially available chest tubes. The 1 control arms consist of consecutively enrolled cardiac surgery patients receiving ≤ four (4) commercially available standard chest tubes. In all arms, one (1) chest tube must be placed in the anterior mediastinum. The other chest tube(s) may be placed at the discretion of the operator. Chest tubes with internal diameter 28 FR to 32 FR shall be used.

2.6 ***Study Population:***

-Up to 508 evaluable post-cardiac surgery female and male subjects, 18 years of age and older will be consecutively enrolled in the study.

- Subjects are required to meet all inclusion criteria and none of the exclusion criteria to be included in this PMCF study. Subjects must be informed about this study and a written and signed informed consent must be obtained from the subject prior to cardiac surgery.

2.7 ***Number of Subjects/sites:***

Up to 508 evaluable subjects enrolled at the Montreal Heart Institute and Sacré-Coeur of Montreal Hospital

2.8 ***Gender/Age:***

Females and males, 18 years of age and older.

2.9 ***Inclusion Criteria:***

Subjects will be required to meet all Inclusion Criteria:

1. Admission for CABG, valve replacement or valve repair surgery, or a combination of these surgeries;
2. Surgical procedure(s) on the ascending aorta and/or aortic arch that do not require deep hypothermic arrest (deep hypothermic arrest is defined as ≤ 14° C);
3. Must be in sinus rhythm (SR) for a minimum of 30 days prior to the index surgery **and** at the start of the index surgery. No patient with history of atrial fibrillation.
4. Sign the IRB/IEC approved informed consent form after the nature of the study has been explained and questions/concern have been addressed.

2.10 ***Exclusion Criteria:***

Subjects will be required to meet none of the exclusion criteria:

1. Admitted for surgical treatment of arrhythmia or Atrial fibrillation history;
2. Admitted for cardiac surgery requiring implantation/explantation of a Ventricular Assist Device (VAD) or heart transplant;
3. Admitted for Transcatheter aortic valve replacement (TAVR);
4. Cardiac surgical procedure that requires deep hypothermic arrest (as defined above);
5. New or active endocarditis or myocarditis that is not adequately controlled with medication and/or requires surgical intervention;
6. Documented inherited bleeding disorder(s);
7. History or known allergies to the device materials; or
8. Participation in another clinical investigation. If a subject has recently completed participation in another drug or device clinical investigation, the subject must have completed that study at least thirty (30) days prior to being enrolled in this clinical study.

2.11 ***Device:***

ClearFlow's PleuraFlow® Catheter System

2.12 ***Indications for Use:***

The PleuraFlow® ACT® System is indicated for use as an adjunctive device during open surgical procedures in order to prevent fluid accumulation within the operative site after closure of the surgical wound. The device is indicated for use in cardiothoracic surgical procedures.

2.13 ***Endpoints:***

2.13.1 Primary performance endpoint

- Rate of any episode of new onset of Post-Operative Atrial Fibrillation (POAF) in the study group. POAF is defined as any atrial fibrillation episode ≥ 60 min on telemetry or EKG. At any time between post index surgery through hospital discharge.

2.13.2 Secondary performance endpoints

- Rate of interventions to treat Retained Blood Syndrome (RBS). RBS is a composite endpoint defined as an intervention to treat one or more of the following conditions:

  -Re-exploration for bleeding, tamponade or washout of retained blood [Time Frame: discharge from OR to 30 days post index surgery];

  -Any procedure to treat Pericardial effusion; i.e., pericardial window, pericardiocentesis, placement of pericardial drain [Time Frame: discharge from OR to 30 days post index surgery];

  -Any procedure to treat Pleural effusion; i.e., thoracentesis under any image-guided modality [Time Frame: discharge from OR to 30 days post index surgery];

  -Any procedure to treat hemothorax (i.e., chest tube, thoracoscopy, thoracotomy, etc.) [Time Frame: discharge from OR to 30 days post index surgery]Any procedure to treat Pneumothorax. [Time Frame: discharge from OR to 30 days post index surgery].

- Readmission for any diagnosis of RBS and/or POAF-related occurrences [Time Frame: within 30 days post index surgery].

- Readmission for any reason. [Time Frame: within 30 days post index surgery].

2.13.3 Other Outcomes:

- Mortality [Time Frame: within 30 days post index surgery];
- Length of Hospital Stay [Time Frame: day of discharge];
- Stay in the Intensive Care Unit (ICU) [Time Frame: hours];
- Ventilation time [Time Frame: hours to extubation];
- Transfusion postoperative [Time Frame: total number and type of units used];
- Total chest tube output first 24 hours [Units: milliliters];
- Total chest tube drainage [Units: milliliters];

- Any cardiac arrest [Time Frame: within 30 days post index surgery];
- Stroke [Time Frame: within 30 days post index surgery];
- Renal failure requiring dialysis [Time Frame: within 30 days post index surgery];
- Renal insufficiency with serum creatinine level 3 times greater than baseline level or serum creat level $\geq$ 300 μmol/L. [Time Frame: within 30 days post index surgery]; converter en umol/L pour nous.
- Surgical Site Infection:

-Sternal Superficial Wound Infection: (i) within 30 days post index surgery; (ii) 30 days post index surgery but during hospitalization; (will be confirmed at postoperative surgeon appointment)

-Deep Sternal Infection/Mediastinitis; within 30 days post index surgery (will be confirmed at postoperative surgeon appointment)

-Post-op Pneumonia; within 30 days post index surgery (will be confirmed at postoperative surgeon appointment)

- Septicemia [Time Frame: hospital discharge];
- Sepsis [Time Frame: within 30 days post index surgery];
- Urinary tract infection [Time Frame: within 30 days post index surgery];

2.14 *Data Management:*

Data will be collected and stored at the department of surgery of Montreal Heart Institute. Only the principal investigator and study coordinators will have access to the database.

2.15 *Statistics*

Sample Size Calculations:

The primary analysis will be an intention-to-treat (ITT) analysis comparing the POAF rate in the PleuraFlow® group to the POAF rate in the control group. Based on findings from our institutional clinical database at the Montreal Heart Institute, the local incidence of POAF after cardiac surgery is approximately 25% (control group). The proportion in group Pleuraflow (the treatment group) is assumed to be 0,2500 under the null hypothesis and 0,1500 under the alternative hypothesis. Group sample sizes of 254 in each group achieve 80% power to detect a difference between the group

proportions of 0,1000 using a Chi-Square test with a significance level of 0.0476. This significance level is computed using the O'Brien-Fleming method and accounts for the interim analysis that is planned after 300 randomized subjects have completed their 30-day follow-up.

Statistical Analysis

POAF and intervention to treat RBS rates and all other categorical event rates will be compared using chi-square tests. Multiple logistic regressions to adjust for potential confounding factors will also be used. Odds ratio and associated 95% confidence intervals will be computed for descriptive purpose. Goodness of fit will be checked using Hosmer-Lemeshow statistics. Quantitative endpoints will be investigated using Student t-tests. Analysis of covariance may also be used to account for potential confounding factors. Nonparametric tests or data transformation may be used if quantitative endpoints are not normally distributed. Correlations and associated 95% confidence intervals will be computed for descriptive purpose.

An interim analysis will be conducted on the first 300 randomized subjects completing their 30-day follow-up. The primary endpoint (POAF rate) will be compared between the PleuraFlow® group and the control group using a chi-square test. The significance level for this test will be 0.0076, as computed using the O'Brien-Fleming method. If the p-value of the chi-square test is below this bound at the interim analysis, the study will be stopped for efficacy. Otherwise, the study will continue up to the planned 508 patients. As a result of this interim look, the final analysis of the primary endpoint would require a $p < 0.0476$ to be declared statistically significant. Analysis of the secondary endpoints and other outcomes will be conducted at the 0.05 significance level.

Signature Page

Active Clearance Technology® Improves Patient Outcomes and Reduces Post Operative Atrial Fibrillation- The ACT POAF Trial

Investigator's Signature

I have read this study protocol. I agree to comply with its written requirements; I agree to follow reporting requirements in accordance with 21CRF part 806, MEDDEV 2.12/1 rev 8 Guidelines on a Medical Devices Vigilance System, MEDDEV 2.12/2 rev 2 Post Market Clinical Follow Up studies, Health Canada Medical Device Regulations SOR/98-282, HIPAA requirements, the Declaration of Helsinki and the following International Harmonized Standards: ISO 14155:2011 (E), and with applicable State, Country and conditions imposed by the reviewing Ethical Committee.

P Demers 16/03/07

Investigator's Signature **Date**

P Demers

Print Name

3 Abbreviations and Definitions

Table 1 Abbreviations and Explanations

Term	Definition
ACT	Active Clearance Technology
AFib	Atrial Fibrillation
CABG	Coronary Artery Bypass Graft
CFR	US code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CVA	Cerebrovascular Accident
IEC	Independent Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clincial Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFU	Instructions for Use
NIS	US National Inpatient Sample
IRB	Institutional Review Board
ITT	Intent to Treat
MDR	Mandatory Medical Device Reporting (US)
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PF-CA	PleuraFlow Clearance Apparatus
PF-CT	PleuraFlow Chest Tube
PMCF	Post Market Clinical Follow-up Study
PHI	Personal Health Information
POAF	Postoperative Atrial Fibrillation
PP	Per Protocol
RBS	Retained Blood Syndrome
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
VAD	Ventricular Assist Device
VTE	Venous Thromboembolism
WBC	White Blood Count
WMA	World Medical Association

4 Background and Rationale

Post Operative Atrial Fibrillation (POAF) is one of the most common complications after heart surgery, occurring in 20% to 60% of patients, and is a leading cause of hospital costs and readmissions.[1] Based on findings from our institutional clinical database at the Montreal Heart Institute, the local incidence after cardiac surgery is approximately 25%. In the NIH POAF study, the Montreal Heart Institute result's show an incidence of 35% of POAF (33/95 recruted patient). POAF is associated with an increased risk of mortality and morbidity, predisposes patients to a higher risk of stroke, requires additional treatment, and increases the costs of the post-operative care.[2] There are currently no reliable preventative approaches that can be uniformly applied to all patients in a prophalactic fashion to reduce this complication. Various drug regimins have been tested, but must be selectively applied and can have undesirable side effects.[3] The development of a universally applicable prophalactic approach that reduces POAF broadly would be a great advance for cardiac surgery patients.

Although the etiologiy of POAF is likely multifactorial, recent evidence suggest that inflammation around the heart during recovery may play a role in the development of POAF.[4, 5] Unevacuated retained blood is a common finding, which has been postulated as driving an inflammatory response around the heart during early recovery.[2, 6] Retained blood occurs when shed blood is incompletely evacuated from around the heart after surgery. When patients bleed in the early hours after heart surgery, reliable postoperative blood evacuation of the pleural, mediastinal and pericardial spaces with chest tubes is imperative to facilitate pulmonary reexpansion and mediastinal decompression as the patient recovers. When blood encounters the artificial surfaces of chest tubes, the coagulation cascade is initiated, which often leads to partial or complete chest tube obstruction. In a recent study of postoperative cardiac surgery patients at the Cleveland Clinic, 36% of patients were found to have evidence of chest tube obstruction.[7] Chest tube clogging can lead to inadequate evacuation of shed blood in the mediastinal or pleural spaces, termed Retained Blood Syndrome (RBS).[6] RBS is the presence of postoperative pericardial and/or pleural blood that is diagnosed and may necessitate drainage of bloody effusions in the acute or subacute setting. Patients with occluded chest tubes have been shown to have a higher rate of POAF, suggesting a link between occluded chest tubes, the development of RBS and POAF.[7]

Clinical studies reinforce this link by demonstrating that more complete postoperative drainage of the pericardium reduces the incidence of POAF.[8, 9] In a prospective study, Ege and colleagues demonstrated a reduction in POAF from 23.8% to 11.3% by employing a redundant multi-drainage tube strategy to reduce retained blood.[10] In a similar study, Eryilmaz and colleagues reduced the incidence of POAF from 32.7% to 10.4% with a protocol aimed at minimizing retained pericardial blood early after operation.[10] In all of these studies, there appears to be a link between bloody pericardial effusions and development of POAF. While the precise mechanism behind this effect is unclear, reduced inflammation from minimizing retained blood and clot in the pericardium may be contributory.[8, 9]

Chest tube clogging has long been a concern in early post operative recovery.[11] Methods such as chest tube stripping or milking, or opening chest tubes to remove clots with balloon catheters have been utilized but have been shown to be ineffective and possibly even harmful, leading to a significant unmet need on how to best maintain chest tube patency after surgery.[12-14] Preventing chest tube occlusion to facilitate

maximal drainage of blood around the heart in the early hours of recovery after cardiac surgery has the potential to alleviate this problem. The PleuraFlow® System with Active Clearance Technology® (ClearFlow Inc. Anaheim, CA), was developed by surgeons to facilitate postoperative blood evacuation by preventing chest tube occlusion.[11] This system, which is placed in the operating room at the end of the procedure, is utilized in the ICU to prevent chest tube occlusion in the first 24 hours or until the patients stops bleeding during early recovery. PleuraFlow was shown in pre-clinical studies to be highly effective in preventing RBS.[15, 16] After initial regulatory approval, Montreal Heart Institute was the site of the world's first human use of this technology. All the surveyed surgeons noted that the device was not any more difficult to insert than a conventional chest tube and was easy to assemble and use. A majority of surveyed nurses felt that the device was more time efficient than stripping, milking, or tapping the chest tubes to keep them open and felt it represented an easy to implement solution to the common problem of chest tube clogging.[17] In a subsequent study, it has been reported that the use of PleuraFlow in a universal use protocol significantly reduces RBS and POAF. Study results showed a statistically significant 42% reduction in re-interventions for RBS complications among a 256 patient cohort where the PleuraFlow® system was used prospectively in comparison to a 1,849 historical cohort. Additionally, there was a statistically significant 30% decrease in POAF documented in the treatment group versus the historical control.[18]

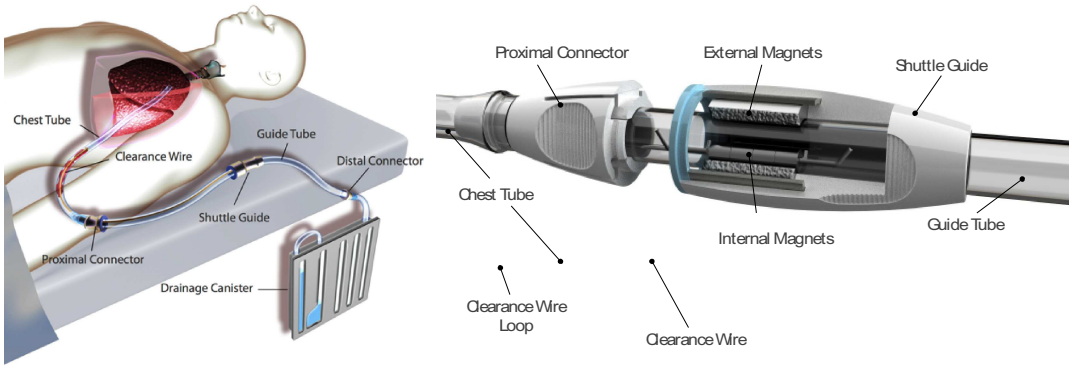
Given the findings that this device has already been shown to be readily implemented into our work flow in the ICU in a preliminary published study, and the new findings of reduced POAF and RBS, the purpose of this study is further evaluate these findings in a randomized controlled setting. Therefore, we hypothesize that active clearance of chest tubes to optimize evacuation of shed mediastinal blood in the immediate postoperative period will reduce the incidence of re-interventions for POAF and RBS and lower overall morbidities after cardiac surgery. Should this prove to be a valid hypothesis, protocols to keep chest tubes patent in the early hours after cardiac surgery can be developed and implemented.

5 Device

The PleuraFlow® system is a commercial product regulatory cleared in the United States (US) (K093565) and by Health Canada. It will be used according to indications for use and the current Instructions for Use (IFU).

The PleuraFlow® Active Clearance Technology® System consists of a PleuraFlow® chest tube (PF-CT) and PleuraFlow® Clearance Apparatus (PF-CA). Together these two pieces make up the PleuraFlow® System. The device incorporates an integrated internal tube Clearance Apparatus designed to maintain patency of the chest tube, thus enhancing fluid evacuation from the thoracic cavity. The active mechanism consists of an external to internal magnetic coupling that controls the movement of a metal wire inside the chest tube. Movement of the internal wire to clear the chest tube is actuated externally, without breaking the internal sterile field (see Figure 1). The PleuraFlow® ACT® has been tested in an experimental animal model at the Cleveland Clinic.[1)12] In a head to head comparison with a same sized conventional 32 Fr chest tube in the setting of heavy bleeding, the PleuraFlow® drained significantly more, and significantly prevented residual hemothorax.[1)13] When the 20 Fr minimally invasive system was tested against a 32 Fr conventional tube, again there was significantly superior drainage and significantly less retained blood and clot with the PleuraFlow® System. This was the first time a small diameter drainage tube was found to be superior to a larger diameter tube.[1)14] During initial clinical use physicians and nurses rated the PleuraFlow® system positively for its ability to be incorporated into the postoperative workflow of managing the drainage of patients after heart surgery.[1)15]

Figure 1: The PleuraFlow® ACT® System Overview



6 Indications for Use and Contraindications:

6.1 Indications

The PleuraFlow® ACT® System is indicated for use as an adjunctive device during open surgical procedures in order to prevent fluid accumulation within the operative site after closure of the surgical wound. The device is indicated for use in thoracic surgical procedures.

6.2 Contraindications

The PleuraFlow® System is contraindicated for patients with a history of intolerance to implantable silicone materials.

7 Good Clinical Practice

This clinical investigation will be conducted in compliance with regulatory requirements intended to:

- Protect the rights, safety and well-being of human subjects;
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results;
- Define the responsibilities of the manufacturer and principal investigator, and;

Assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved on the conformity assessment of medical devices.

8 Study Design

This is a prospective, randomized, two-arm, single blinded, single-center Post Market Clinical Follow-Up (PMFC) study. An interim analysis allowing for an early look at efficacy is planned after 300 randomized subjects have completed their 30-day follow-up. This interim analysis is proposed following the results of a retrospective study done at the Montreal Heart Institute on more than 300 patients, comparing AF rate between patients with pleuraflow and control patients. After a propensity score adjustment, a difference of 16% was obtained (AF rate of 9% in the pleuraflow group vs 25% in the control group). Since this might be a sign that the difference between the two arms is larger than expected, an interim analysis is planned after 300 patients.

8.1 Test Arm

The test arm consists of consecutively enrolled cardiac surgery patients receiving $\leq$ two (2) PleuraFlow® chest tubes with Active Clearance Technology® and $\leq$ two (2) other commercially available standard chest tubes.

8.2 Control Arm

The control arms consist of consecutively enrolled cardiac surgery patients receiving $\leq$ four (4) commercially available standard chest tubes.

8.3 Control and Test Arms

In all arms, one (1) chest tube must be placed in the anterior mediastinum. The other chest tube(s) may be placed at the discretion of the operator. Chest tubes with internal diameter 28 FR to 32 FR shall be used for the single anterior mediastinal chest tube.

The Montreal Heart Institute is required to participate in a pre-study roll-in phase prior to participating in this clinical study. The purposes of the pre-study roll-in phase are to:

- Allow the users at participating sites to familiarize themselves with the product use and with ACT;
- Implement Clinical Use Protocols provided by ClearFlow, Inc. to all commercial users as part of product training, and;
- Demonstrate consistency and compliance with the clinical use protocols.

Pre-study roll-in phase requirements are:

- Consecutive use of PleuraFlow® system on patients having cardiac surgeries during a 1 month period.

9 Study Population

9.1 Demographics

-Up to 508 evaluable post-cardiac surgery female and male subjects, 18 years of age and older will be consecutively enrolled in the study.

- Subjects are required to meet all inclusion criteria and none of the exclusion criteria to be included in this PMCF study. Subjects must be informed about this study and a written and signed informed consent must be obtained from the subject prior to cardiac surgery.

9.2 Inclusion Criteria

Subjects will be required to meet all Inclusion Criteria:

9.2.1 Admission for CABG, valve replacement or valve repair surgery, or a combination of these surgeries. Surgery must be done through a mediansternotomy;

9.2.2 Procedure on ascending aorta and/or aortic arch that do not require deep hypothermic arrest (defined as $\leq$ 14° C);

9.2.3 Must be in sinus rhythm (SR) for previous 30 days prior to the index surgery **and** at the start of the index surgery. No patient with history of atrial fibrillation;

9.2.4 Sign the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved Informed Consent Form after the nature of the study has been explained and questions/concerns have been addressed.

9.3 Exclusion Criteria

Subjects will be required to meet none of the Exclusion Criteria:

9.3.1 Admitted for surgical treatment of arrhythmia;

9.3.2 Admitted for cardiac surgery requiring implantation/explantation of a Ventricular Assist Device (VAD) or heart transplant;

9.3.3 Cardiac surgical procedure that requires deep hypothermic arrest (as defined above);

9.3.4 Admitted for Transcatheter aortic valve replacement (TAVR);

9.3.5 New or active endocarditis or myocarditis that is not adequately controlled with medication and/or requires surgical intervention;

9.3.6 Documented inherited bleeding disorders;

9.3.7 History or known allergies to the device materials; or

9.3.8 Participation in another clinical investigation. If a subject has recently completed participation in another drug or device clinical investigation, the subject must have completed that study at least thirty (30) days prior to being enrolled in this clinical study.

10 Procedural Steps and Methods

This study is on label and, accordingly, there are no specific procedures to follow. The test article (PleuraFlow® System) will be used at the end of the cardiac surgery per standard of care. The Sponsor is blinded to the study results. Data will be revealed to the Sponsor after the last enrolled subject has exited the study (end of postoperative day 30 or hospital discharge, whichever occurs last).

10.1 Informed Consent and Subject Enrollment

Investigators shall obtain a signed informed consent from each subject before enrolling as a study subject. Each subject shall sign and date the IRB/IEC approved Informed Consent Form (ICF). A subject who is unable to read and/or provide signature can participate in this clinical study, provided that a legal representative with signature authority signs and dates the ICF on behalf of the subject.

Subjects shall be given sufficient time to review the ICF and ask questions before signing. The investigator or designee shall be available to answer any questions about this clinical study. An independent witness shall be present during the consenting process, and will sign and date the ICF.

The device and procedures that are part of this PMFC study are performed after a scheduled cardiac surgery and are part of routine standard of care. There are no procedures or treatments that are required for the purposes of the study. The research part of the study is the data collection of subjects' history, peri- and post-cardiac surgery and postoperative clinical appointment.

10.2 Screening and Enrollment

Participating sites shall screen consecutive patients who are admitted for cardiac surgery. Patients who could meet the study eligibility criteria will be offered to participate in this clinical study. Screen failures and reason(s) for screen failure shall be documented on study-specific logs and provided to the Sponsor periodically.

Patients who meet the clinical study eligibility criteria and sign the ICF shall be enrolled and randomized prospectively ***before*** surgery to either receive the test article (PleuraFlow® System) and other commercial chest tubes (test arm), or to receive commercial chest tubes only (control arm), as part of their cardiac surgery (day 0). Any commercial chest tube is eligible for use in this clinical study. Enrollment period is from consent through 30 days post index surgery.

10.3 Training

Product Training

Prior to initiation of the trial, a ClearFlow, Inc. representative will train the surgeons and the supporting staff in the operating room and in the intensive care unit (ICU) using a training curriculum.

The device shall be used according to the commercial IFU (Manual of Operations). ClearFlow, Inc. has created Clinical Use Protocols (Manual of Operations) for the use of PleuraFlow® ACT®. The Clinical Use Protocols are in accordance with the IFU. Users will follow the specific procedural steps outlined in the attached commercial Clinical Use Protocols (Manual of Operations).

Placement (locations) and number of PleuraFlow® System(s) and commercial chest tubes are dictated by this PMCF study protocol (See section 6).

10.4 Documentation

Training will be documented. The trainee must sign and date the training record. Training must be completed and training records must be signed and dated before the staff is allowed to perform specific clinical investigation related tasks delegated to them by the PI.

10.5 Randomization

Subjects who meet eligibility criteria will be randomly assigned in a 1:1 fashion to either the Test arm or the Control arm.

The point of randomization is before the start of the index surgery. Subject assignment will be provided to the operating surgeon at that time.

10.6 Follow-up Assessment

Subjects will exit the study at the end of postoperative day 30 (midnight). Clinical data will be collected through 30 days post index surgery. This will include re-admission for diagnosed POAF and/or RBS related occurrences within 30 days after the index surgery. The patient will be considered as exited from the study at end of day 30 (midnight) post index surgery for the purposes of clinical data collection.

10.7 Study Termination

Subject participation is terminated at day 31 post index surgery.

If a subject is re-admitted within 30 days after the index surgery to the treating hospital, a satellite clinic, or another hospital for any diagnosis of RBS and/or POAF-related occurrences, clinical data will be collected.

Table 2: Subject participation and data collection period

	Discharge <30d*	Discharge >30d
Clinical data	Y	N

* Including re-admission for RBS and/or POAF-related occurrences <30d.

11 Safety Assessment and Medical Device Reporting

The PleuraFlow® System is a Class II device in the US and approved device in Canada and a Class IIa device per rule 7 of Annex IX of Directive 93/42/EEC. In its issuance of a substantial equivalence determination, the FDA did not require Sponsor to conduct a PMCF study. This PMFC study is conducted on label. Being marketed also in the European Community (EC), this study has to meet post-market surveillance requirements. In the preface of MEDDEV 2.12/2 Rev 2 "Post Market Clinical Follow-Up Studies, A Guide for Manufacturers and Notified Bodies" it is stated: "Similarly when PMCF studies are conducted using CE Marked devices within their intended use, the provisions of Section 2.3.5 of Annex X of Directive 93/42/EEC do not apply. However, the provisions of Directive 93/42/EEC concerning information and notification of incidents occurring following placing devices on the market are fully applicable.

Sponsor is subject to all requirements of 21 CFR Part 803 (MDR Reporting). Accordingly, Sponsor shall report all MDR reportable events (see definition) to FDA on Form FDA 3500A. Sponsor shall review and evaluate all complaints (see definition) to determine whether a complaint represents an event that must be reported to FDA. Sponsor shall report an event upon becoming aware of information that reasonably suggests that the PleuraFlow® System has or may have caused or contributed to a death, serious injury, or has malfunctioned and that the device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Serious injuries where the device would be likely the cause of or contributed to shall be followed to resolution.

The PI will evaluate and determine if the PleuraFlow® System has or may have caused or contributed to a death, serious injury, or has malfunctioned. Sponsor has the right to request the steering committee to review the PI decision and concur or disagree. In case the steering committee and PI disagree the steering committee adjudication prevails.

11.1 Definitions

Serious injury /(Serious illness) [21 CFR part 803.3(aa)(1)] is an injury or illness that:

- is life threatening, even if temporary in nature;
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A malfunction [21 CFR Part 803.3(m)] is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. A malfunction should be considered reportable if any one of the following is true:

- the chance of a death or serious injury occurring as a result of a recurrence of the malfunction is not remote;
- the consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury;
- it causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness, which could cause or contribute to a death or serious injury, or other significant adverse device experiences. The essential function of a device refers not only to the device's labeled use, but for any use widely prescribed within the practice of medicine;

- it involves an implant malfunction that would be likely to cause or contribute to death or serious injury, regardless of how the device is used;
- the device is considered life-supporting or life-sustaining, and thus essential to maintaining human life; or

11.2 Reporting Requirements

Investigators shall report to Sponsor PleuraFlow-related serious injuries as soon as becoming aware of the injury and no later than 48 hours.

Investigators shall report deaths to both the Sponsor and Regulatory authorities in compliance with their applicable State, Country and conditions imposed by the reviewing Institutional Review Board (IRB).

Sponsor shall take action under 21 CFR part 518 or part 806 of the FD&C Act as a result of the malfunction of the device.

Sponsor shall also take action under MEDDEV 2.12/1 rev 8 Guidelines on a Medical Devices Vigilance System and under Health Canada Medical Device Regulations SOR/98-282, since the device is marketed under a CE Marking and Health Canada license.

Sponsor's reporting requirements are listed in Table 3.

Table 3: Manufacturer's Reporting Requirements and Timelines

PleuraFlow® System: A) is marketed in the US B) has Canadian License C) has CE marking	**US MDR Action File MedWatch Report (form 3500A) to FDA**	**EU-MDV Action File Vigilance SystemReport**		**Canadian MPR Action File Mandatory Problem Report**	
		Incident occurred in EEA	**Incident occurred outside EEA**	**Incident occurred in Canada**	**Incident occurred outside Canada**
and…	**Reporting Timeframe for 2, 5, 10, & 30 day reports, start the day after the first Company employee is notified. Report is to be sent within the time specified below.**				
a **malfunction** were to occur that requires immediate remedial action to prevent an unreasonable risk of substantial harm to the public health (or as described in MEDDEV 2.12-1 for the EU, Serious Public Health Threat).	Yes Initial Report 5 working days	Yes Initial Report immediately but not more than 2 calendar days	Yes Initial Report immediately but not more than 2 calendar days*	Yes On or before recall actions initiated; immediately without any delay which cannot be justified for serious public health issues	Yes On or before recall actions are initiated for any corrective action; immediately without any delay which cannot be justified serious public health issues
The **FDA** has identified an event, and submitted a written request to file a report, for all subsequent events of the same nature that involve similar devices for a specified time period.	Yes 5 working days	N/A	N/A	N/A	N/A
FDA and CMDR Information reasonably suggests a death or serious injury /	Yes 30 days	NA	NA	Yes Preliminary	Yes Preliminary

deterioration of health has occurred and was caused or contributed to by a device manufactured by our company.				Report immediately without any delay which cannot be justified and not more than 10 days	Report immediately without any delay which cannot be justified and not more than 10 days if corrective action is initiated
MDD Information reasonably suggests a death or **unanticipated** serious deterioration of health has occurred and was caused or contributed to by a device manufactured by our company.	NA	Yes Initial Report immediately but not more than 10 calendar days	No	NA	NA
A malfunction has occurred with the PleuraFlow® System and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.	Yes 30 days	Yes Initial Report immediately but not more than 30 calendar days	No	Yes Preliminary Report immediately without any delay which cannot be justified and not more than 30 days	Yes Preliminary Report immediately without any delay which cannot be justified and not more than 30 days if corrective action is initiated
Additional information becomes available after the initial report has been submitted.	Supplemental Report	Final Report	NA	Final Report	Final Report
A systematic Recall has been initiated due to risk of Death or Serious Injury (reported to a Regulatory Agency)	Yes Submit Report Within 10 working days of initiating action	Yes On or before initiating recall actions	Yes On or before initiating recall actions	Yes Before and after initiating recall actions	Yes On or before recall action; indicating to or requested to take such actions by a Regulatory Agency

12 Data

Data is collected on Case Report Forms (CRFs). Electronic Data Capture (EDC) system will be used to enter data. Manual (paper) CRF samples are provided in the study Manual of Operation.

Source data shall be used to complete the study CRF. Source data consist of all information in the patient health record with the exception of Personal Health information (PHI). These include hospital records, records from doctor office visits, clinic visits, hospital re-admission after discharge and up to 30 days after the index surgery, laboratory results and clinical staff notes.

Source documents, if not in electronic format, should be completed legibly, in dark ink, typewritten or generated by testing equipment. Any necessary corrections should be made by a single strikethrough in ink, initialed and dated by the person who makes the change on the day the change is made.

Upon CRF completion, the Investigator should sign and date each CRF that bears a signature line. Completed CRFs shall be monitored and collected during periodic site visits. Source documents and copies of CRFs shall be available for review by the study sponsor, monitor and authorized regulatory bodies.

12.1 Protection of Patient Privacy and Confidentiality of Patient Information

The PMCF study will be conducted in accordance with GCP. Subject confidentiality shall be maintained at all times throughout the conduct of this trial and all subject data shall be maintained secure against unauthorized access. Possible review and photocopying of the subject's records by the IRB, Health Canada or FDA representatives could occur. In addition, ClearFlow, Inc., the manufacturer, and its representatives will review and photocopy anonymized subjects' records as part of monitoring activities aimed at assuring the accuracy of the data collected from the subject health record per requirements of this study protocol.

All data entered into the database are anonymized. Patient Health Information (PHI) will not be collected.

Identifiable information of all subject records to be reviewed per the above must be blacked out (de-identified) and only the subject's study number used as tracking information. Individual subject's data will not be used for educational, presentation and/or publication purposes.

Photographs of the chest tubes used in this study may be taken after removal from the patient to document chest tube patency.

Regulatory agencies and ClearFlow, Inc. are required to maintain the privacy of all records they review in connection with this study.

The user interface to the EDC is password protected. Only approved site personnel, trained on the use of EDC will be allowed password-protected access to the EDC for the purpose of data entry. All study documents and data elements will identify patients by their unique subject identification (ID) number.

12.2 Data Monitoring

Trained monitors will conduct periodic site monitoring visits. Purpose of the visits is to verify that data entered to the study database matches the source data. Monitors will coordinate visits with the site personnel.

12.3 Premature Study Termination

In case the study is terminated prematurely, all subjects who have signed an informed consent, and were randomized to the test arm or to the control arm will be considered to have *enrolled* in the study. Subjects who complete the 30 day or index surgery/discharge (whichever occurs later) will be considered to have *completed* the study. The reason for study discontinuation should be documented for each subject.

12.4 Close Out Activities

Study close out activities include, and are not limited to the following documentation.

-Data is entered into the database

-All data queries are resolved

-Regulatory and study specific documents and forms are in order

-MDR reporting is complete

-Communication to Principal Investigator on record retention, final report to IRB/EC, and potential regulatory audits.

12.5 Data Management

Data will be collected and stored at the department of surgery of Montreal Heart Institute. Only the principapal investigator and study coordinators will have access to the database.

12.6 Record Retention

Record will be retain for a period of 5 years in the department of cardiac surgery of the Montreal Heart Institute.

13 Investigator Responsibilities

The Principal Investigator participating in this PMCF study must be a licensed physician in his/her state of employment. The investigator will affirm by his/her signature on this study protocol and the Investigator's Agreement that s/he will fulfill her/his responsibilities relative to this clinical investigation.

The principal investigator shall:

13.1 Obtain IRB/IEC approval to conduct this PMCF study. Principal Investigator shall provide Sponsor with a written IRB approval of the study protocol and patient informed consent.

13.2 Adhere to its institutional, local and FDA rules and regulations regarding release of patient data.

13.3 Ensure that data is entered to the database in accordance with this protocol.

13.4 Ensure that all subjects sign and date the IRB/IEC approved ICF prior to performing any study-related procedures and that subjects entering the study conform to the study eligibility criteria.

13.5 Ensure that during the term of trial set forth in the clinical trial agreement, the Investigators engaging in the trial do not initiate any other clinical trial, which may affect recruitment of subjects for this trial;

13.6 Ensure that qualified, instructed personnel and infrastructure e.g., documentation facilities, etc. are available for the trial and that the trial may also in other respects be conducted in safe conditions;

13.7 Ensure that the Investigators are familiar with the details of the protocol and other liabilities and responsibilities defined in the clinical trial agreement, and that Investigators are committed to act accordingly;

13.8 Ensure that the subjects are not simultaneously involved in any other clinical trials and that they are not subjects to any investigations differing from the trial protocol

13.9 Comply with reporting requirements outlined in Section 12.2.

13.10 Submit patient screening logs to Sponsor.

13.11 Allow monitoring and auditing at the trial site to be conducted by the SPONSOR /SPONSOR representative, as well as US regulatory authorities, and, if necessary, to assist in the executing thereof.

13.12 The Investigator should archive all documents relating to the trial (source documents) at the site for a period of 5 years. In case the Investigator leaves the institution, it must be handed over to the successor.

13.13 Submit progress reports to the Sponsor. A progress report shall summarize the number of enrolled patients and the number of CRFs with entered data that were transmitted/entered to the study data repository. The progress report shall also document complaints reported by the site.

13.14 Maintain trial records for a period of 5 years

13.15 Maintains study-related correspondence with IRB/IEC, FDA, sponsor and sponsor designees.

13.16 Register the trial on www.clinicaltrials.gov before starting the patient recruitment;

13.17 ***Inform the sponsor of the completion of the trial.***

14 Sponsor's Responsibilities

The Sponsor of this PMCF study is ClearFlow, Inc. of Anaheim, CA, U.S.A. and the research found of the Montreal Heart Institute Cardiac surgery department. The Sponsor is committed to:

14.1 Conduct a site initiation visit after IRB/IEC approval of this investigational plan

14.2 Maintain compliance with all applicable regulations;

14.3 Protect the rights, health, safety and welfare of study subjects; the Sponsor is responsible for obtaining and reviewing copies of IRB or IEC approval documents and will verify that appropriate subject informed consent has been obtained;

14.4 Investigate all adverse events, determine reporting requirements and report to all applicable regulatory bodies worldwide, where the PleuraFlow® System is distributed. Report such events in accordance with 21CRF part 806, MEDDEV 2.12/1 rev 8 Guidelines on a Medical Devices Vigilance System, MEDDEV 2.12/2 rev 2 Post Market Clinical Follow Up studies, Health Canada Medical Device Regulations SOR/98-282, HIPAA requirements, the Declaration of Helsinki and the following International Harmonized Standards: ISO 14155:2011 (E), and with applicable State, Country and conditions imposed by the reviewing Ethical Committee;

14.5 Provide the investigational Site with the necessary background information needed for the appropriate and safe conduct of the trial;

14.6 Inform the principal investigator of any new information about the study that may affect the health, safety or welfare of the subjects or which may influence their decision to continue participating in the study;

14.7 Contribute to the statistical analysis and study report-writing resources necessary to complete reporting of the study results;

14.8 Maintain all study documentation, including but not limited to, copies of correspondence, adverse events, customer complaints, records related to the signed investigator agreements and other records related to the clinical study;

14.9 Ensure necessary training and orientation of the investigators and other personnel of the investigational site involved in the trial in order to conduct the trial in accordance with the protocol and good clinical practice requirements. Per the study protocol, training in the use of the PleuraFlow® System and case support are provided during the pre-enrollment phase 1 and subsequently, as necessary.

15 Publication policy

At the conclusion of this study, a manuscript (or manuscripts) shall be prepared for publication in a peer-reviewed scientific journal. Analyses for the publication will be generated from the study database. The PI will oversee the publication.

The clinical site has the right, consistent with academic standards, to publish their study results. This right is subject to this study agreement. The clinical study site agrees to submit any form of publication to ClearFlow, Inc. for review and approval prior to any submission but retains final approval over decisions related to content and journal for submission.

16 Liability

The PleuraFlow® device is commercially available in the countries of participating sites. Sponsor carries product liability insurance with $5,000,000 aggregate/occurrence limit.

17 Study Committees

17.1 *Steering Committee will:*

The study steering committee will consist of the Study coordination investigator and TBD. The study steering committee will:

-Dr Philippe Demers, MHI;

-Dr Louis P. Perrault, MHI;

-Dr Denis Bouchard, MHI;

-Dr Edward Boyle, Clearflow Inc.

The study interim analysis will be verified by Dr Philippe Demers, MHI, to confirm continuation or end of the study.

18 Bibliography

1. Wynne, R., Botti, M., Copley, D., and Bailey, M. 2007. The normative distribution of chest tube drainage volume after coronary artery bypass grafting. Heart Lung 36:35-42.

2. Christensen, M.C., Dziewior, F., Kempel, A., and von Heymann, C. 2012. Increased chest tube drainage is independently associated with adverse outcome after cardiac surgery. J Cardiothorac Vasc Anesth 26:46-51.

3. Dixon, B., Santamaria, J.D., Reid, D., Collins, M., Rechnitzer, T., Newcomb, A.E., Nixon, I., Yii, M., Rosalion, A., and Campbell, D.J. 2012. The association of blood transfusion with mortality after cardiac surgery: cause or confounding? Transfusion. 2013 Jan;53(1):19-27

4. Boyle, E., AM., G., Cohn, W., Sakwa, M., Reddy, V., and Perrault, L. 2013. The Post Operative Retained Blood Complex: Implications for Patient Recovery After Heart Surgery. Manuscript in Preparation.

5. Light, R.W. 2001. Pleural effusions following cardiac injury and coronary artery bypass graft surgery. Semin Respir Crit Care Med 22:657-664.

6. Light, R.W. 2002. Pleural effusions after coronary artery bypass graft surgery. Curr Opin Pulm Med 8:308-311.

7. Light, R.W., Rogers, J.T., Cheng, D., and Rodriguez, R.M. 1999. Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular Surgery Associates, PC. Ann Intern Med 130:891-896.

8. Light, R.W., Rogers, J.T., Moyers, J.P., Lee, Y.C., Rodriguez, R.M., Alford, W.C., Jr., Ball, S.K., Burrus, G.R., Coltharp, W.H., Glassford, D.M., Jr., et al. 2002. Prevalence and clinical course of pleural effusions at 30 days after coronary artery and cardiac surgery. Am J Respir Crit Care Med 166:1567-1571.

9. Ikaheimo, M.J., Huikuri, H.V., Airaksinen, K.E., Korhonen, U.R., Linnaluoto, M.K., Tarkka, M.R., and Takkunen, J.T. 1988. Pericardial effusion after cardiac surgery: incidence, relation to the type of surgery, antithrombotic therapy, and early coronary bypass graft patency. Am Heart J 116:97-102

10. Clark, G., Licker, M., Bertin, D., and Spiliopoulos, A. 2007. Small size new silastic drains: life-threatening hypovolemic shock after thoracic surgery associated with a non-functioning chest tube. Eur J Cardiothorac Surg 31:566-568.

11. Karimov, J.H., Gillinov, A. M., Schenck, L., Cook, M., Kosty Sweeney, D., Boyle, E.M., Fukamachi, K. . 2013. Incidence of chest tube clogging after cardiac surgery: A single-center prospective observational study. Eur J Cardiothorac Surg In Press.

12. Shalli S, Boyle EM, Saeed D, Fukamachi K, Chhn WE, Gillnov AM The Active Tube Clearance System: A novel Bed Side Chest Tube Clearance Device. 2010, Innovations Vol. 5:42-47

13. Shiose A, Takaseya T, Fumoto H, Aralawa Y, Horai T, Boyle E, Gillinov A, Fukamachi K. Improved Drainage with Active Tube Clearance. 2010, CardioVasc Thorac Surg Vol. 10:685-688

14. Arakawa Y, Shiose A, Takaseya T, Fumoto H, Kim H, Boyle E, Gillinov A, Fukamachi K Superior Chest Drainage with an Active Tube Clearance System:

Evaluation of a Downsized Chest Tube. 2011, Annals of Thoracic Surgery Vol. 91:580-583.

15. Perrault, Louis, Michel Pellerin,Michel Carrier,Raymond Cartier,Denis Bouchard,Philippe Demers, Edward M.Boyle. The PleuraFlow Active Chest Tube Clearance System:Initial ClinicalExperience in Adult Cardiac Surgery. Innovations. 2012;7:354-358.

16. World Medical Association's (WMA's) Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects http://jama.jamanetwork.com/ on 10/21/2013.

References

1. LaPar, D.J., et al., Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg, 2014. 98(2): p. 527-33; discussion 533.

2. Echahidi, N., et al., Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol, 2008. 51(8): p. 793-801.

3. Frendl, G., et al., 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. Executive summary. J Thorac Cardiovasc Surg, 2014. 148(3): p. 772-91.

4. Canbaz, S., et al., The role of inflammation in atrial fibrillation following open heart surgery. J Int Med Res, 2008. 36(5): p. 1070-6.

5. Issac, T.T., H. Dokainish, and N.M. Lakkis, Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. J Am Coll Cardiol, 2007. 50(21): p. 2021-8.

6. Gillinov AM, B.E., Cohn WE, Ley SJ, Fischlein T, Perrault LP., Retained Blood After Cardiac Surgery: A New Look at an Old Problem. Innovations (Phila) 2015. Submitted.

7. Karimov, J.H., Gillinov, A. M., Schenck, L., Cook, M., Kosty Sweeney, D., Boyle, E.M., Fukamachi, K. , Incidence of chest tube clogging after cardiac surgery: A single-center prospective observational study. Eur J Cardiothorac Surg 2013. 44(6): p. 1029-36.

8. Arsenault, K.A., et al., Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev, 2013. 1: p. CD003611.

9. Biancari, F. and M.A. Mahar, Meta-analysis of randomized trials on the efficacy of posterior pericardiotomy in preventing atrial fibrillation after coronary artery bypass surgery. J Thorac Cardiovasc Surg, 2010. 139(5): p. 1158-61.

10. Eryilmaz, S., et al., Effect of posterior pericardial drainage on the incidence of pericardial effusion after ascending aortic surgery. J Thorac Cardiovasc Surg, 2006. 132(1): p. 27-31.

11. Shalli, S., et al., Chest tube selection in cardiac and thoracic surgery: a survey of chest tube-related complications and their management. J Card Surg, 2009. 24(5): p. 503-9.

12. Boyacioglu, K., et al., A new use of fogarty catheter: chest tube clearance. Heart Lung Circ, 2014. 23(10): p. e229-30.

13. Day, T.G., R.R. Perring, and K. Gofton, Is manipulation of mediastinal chest drains useful or harmful after cardiac surgery? Interact Cardiovasc Thorac Surg, 2008. 7(5): p. 888-90.

14. Halm, M.A., To strip or not to strip? Physiological effects of chest tube manipulation. Am J Crit Care, 2007. 16(6): p. 609-12.

15. Arakawa, Y., et al., Superior chest drainage with an active tube clearance system: evaluation of a downsized chest tube. Ann Thorac Surg, 2011. 91(2): p. 580-3.

16. Shiose, A., et al., Improved drainage with active chest tube clearance. Interact Cardiovasc Thorac Surg, 2010. 10(5): p. 685-8.

17. LP, P., et al., The PleuraFlow Active Chest Tube Clearance System: Initial Clinical Experience in Adult Cardiac Surgery. Innovations (Phila), 2012. 7(5): p. 354-8.

18. Sirch, J., Ledwon M, Puśki T, Boyle EM, Pfeiffer S, Fischlein T, Active Clearance of Chest Drainage Catheters Reduces Retained Blood Journal of Thoracic and Cardiovascular Surgery 2015. Submitted.