A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve

Regulatory Sponsor: Dr. K. Robert Shen
Department of Surgery, Division of General Thoracic Surgery
Mayo Clinic
200 First Ave SW
Rochester, MN 55905

(507) 266-0911

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve
Running Title	Discharged with Indwelling Chest Tube and Valve
Protocol Number	17-007774
Phase	Phase II
Methodology	Randomized
Overall Study Duration	5 years
Subject Participation Duration	30 Days
Single or Multi-Site	Multi-Site
Objectives	To assess the efficacy of antibiotics and closer monitoring on decreasing empyema in patients discharging with a chest tube and valve in place as measured by documented empyema following discharge.
Number of Subjects	560
Diagnosis and Main Inclusion Criteria	Discharge from the hospital with an indwelling chest tube and valve in place.
Study Treatment	Oral antibiotics and close monitoring.
Reference Treatment	Standard of Care
Statistical Methodology	Comparison of the rate of empyema and readmission in the two arms of the study.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Prolonged air leak remains a troublesome problem in general thoracic surgery. Many studies have attempted to identify risk factors for prolonged air leak, which include reduced pulmonary function, use of steroids, upper lobectomy, age, decreased body mass index, and the presence of adhesions, however no one factor is highly predictive for air leak or time to leak closure (1-3). Many adjuncts are used intraoperatively to prevent air leaks, but no consistently effective solution has been discovered (4-5). In the era prior to wide adoption of video-assisted thoracic surgery (VATS), patients underwent thoracotomy and remained in the hospital for multiple days until chest tube removal. During this convalescence, many air leaks would seal. However, in the current era characterized by decreased length of stay, avoidance of hospital acquired conditions, minimally invasive thoracic surgery, and enhanced recovery protocols leading to faster return to activities of daily living, the problem of prolonged air leak is more difficult to manage because patients are not necessarily remaining hospitalized. Further, with quality measurements and economic impacts for early discharge, a prolonged air leak is a much more significant issue, since it significantly increases postoperative length of stay and cost (6-9). Many centers have reported managing this issue with dismissal from the hospital with a chest tube in place connected to a one-way valve mechanism (10-13). However, evidence suggests that the risk of empyema increases with prolonged chest tube duration (14-15).

1.2 Clinical Data to Date

Several studies report prolonged air leak rates in the 10-15% range following lobectomy (1-3). Prolonged air leak has been shown to be a primary driver in prolonged length of stay and increased hospital costs (6-9). Varela and colleagues found air leaks longer than 5 days increased rate of pulmonary complications including atelectasis, pneumonia, or empyema (7). Brunelli and colleagues reported an increased rate of empyema of 8.2% to 10.4% in patients with prolonged air leaks lasting more than 7 days versus only 0% to 1.1% in patients with shorter air leaks (14). This study also showed that longer air leaks led to further interventions; however, this was not in patients discharged from the hospital (14).

Dismissal from the hospital with a chest tube in place is not a novel concept. Multiple groups have advocated for this practice. McKenna and colleagues reported on fast-tracking thoracoscopic patients. They utilized this strategy in 2.5% of patients (7/282) and reported only one patient required readmission (12). Another study by Rieger et al. utilized the mini-Atrium® device for dismissal of patients with a chest tube in place for either effusions or air leak. They reported a rate of minor complications in 11% (4/36), which included 3 readmissions, one of which was for an empyema (13). Royer et al. described similar practice with dismissal of 65 patients with a chest tube and Heimlich

valve (13%, 65/496). Two patients were readmitted and 4 had superficial site infections requiring oral antibiotics but no empyema was reported. Overall they reported a potential savings of 305 inpatient hospital days (11). In light of these findings, hospital length of stay is decreased and, concurrently, cost with this practice. These studies encourage the practice with little complications.

Reinersman and colleagues evaluated outcomes of patients discharging with an indwelling chest tube from a high volume referral center. At the institution all patients who are discharged with an indwelling chest tube receive standard education from our nursing staff as to dressing changes, changing the dressing when saturated, and noting daily output and changes in output. All patients are instructed on how to check the device for air leak. If they notice the leak has ceased, they are to call for the next available appointment to be seen in clinic for possible chest tube removal. Additionally, all patients receive a standard dismissal education pamphlet summarizing the care of the chest tube and Heimlich valve or mini-Atrium®. They found that the rate of empyema was 16.5%, using strict criteria, including all patients with a leukocytosis or fever and an undrained effusion on chest x-ray or CT scan. The rate of readmission with a chest tube in place was found to be 25%.

Reinersman and colleagues found male gender, a history of coronary artery disease and peripheral vascular disease were found to be predictors of empyema (15). Traditional predictors of air leak were analyzed including pleural adhesions, chronic obstructive pulmonary disease, upper, age, use of steroids and decreased body mass index (1-3). These traditional predictors did not contribute to risk of empyema and readmission in their study. The number of patients who were on immunosuppressive medications was too small to determine a difference. The presence of diabetes approached significance but was not a major predictor. Examining reoperative surgery as a surrogate for pleural adhesions also did not show a statistically significant difference in rate of empyema or readmission (*p=0.2*) (15).

As previously discussed, Brunelli et al. reported that the presence of an air leak greater than 7 days led to a higher rate of empyema compared to patients without air leak or with a shorter duration air leak (14). Reinersman et al. also revealed a temporal relation to number of days with air leak and chest tube related to risk of empyema. The overall number of days with chest tube in place was found to be a predictor of empyema, with an incremental increase per one day with chest tube (HR 1.2, *p=0.006*). Further, the presence of an air leak and chest tube for more than 14 days markedly increased the risk of empyema (HR 7.6, *p=0.047*) (15).

1.3 Risks and Benefits

All study interventions could be considered standard of care.

Cerfolio and colleagues cite the use of oral antibiotics while the chest drain is in place but they do not address any risks or benefits but state it is merely their preference (3). In the study conducted by Reinersman and colleagues, the 27 patients discharging with indwelling chest tubes in place that received prophylactic antibiotics at discharge were

found to have no complications from the antibiotics (15). Cerfolio, Reinersman and colleagues have reported that an air leak lasting longer than 7 days leads to an increased risk of empyema (14, 15).

The Surgical Care Improvement Project (SCIP) Performance Measures endorse pprophylactic antibiotics discontinued within 24 hours after surgery end-time. There is no significant evidence showing a benefit to continuing antibiotic usage beyond 24 hours. Prolonged administration of antibiotic usage may increase the risk of drug resistance and secondary infections, such as *Clostridium difficile* (16).

2 Study Objectives

Primary Objective

To assess the efficacy of antibiotics and closer monitoring on decreasing empyema in patients discharging with a chest tube and valve in place as measured by documented empyema following discharge.

Secondary Objective

To assess the efficacy of antibiotics and closer monitoring on decreasing hospital readmissions while the chest tube and valve are in place as measured by readmission to the hospital following hospital discharge after the initial surgical intervention.

3 Study Design

3.1 General Description

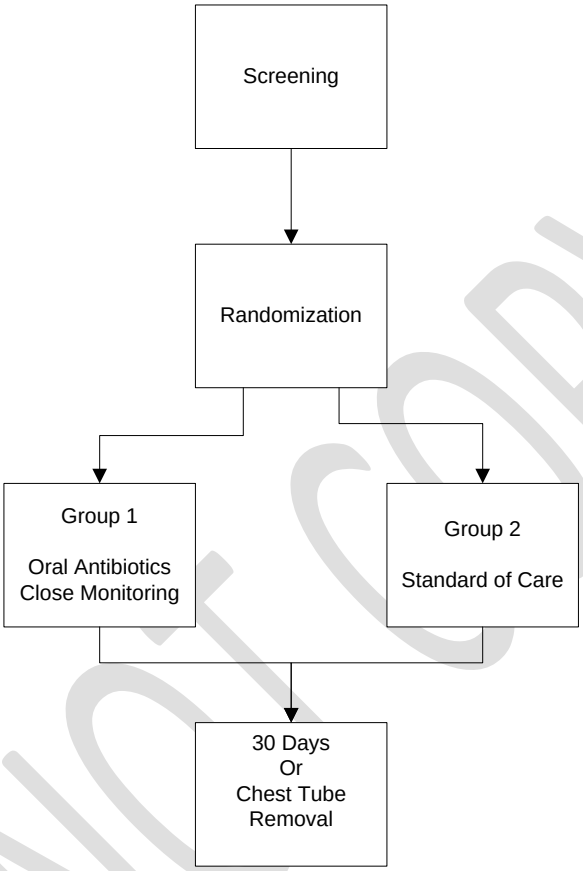
This study is a multicenter, randomized trial for the treatment of subjects discharging from the hospital with a chest tube and valve in place. Subjects will be screened prior to discharging from the hospital and interested qualified subjects will be consented and offered participation in this trial. Once consent has been obtained the subject will be randomized to receive oral antibiotics and close monitoring, defined as twice weekly telephone calls by a member of the care team, of their chest tube and valve or standard of care, defined as no calls from the care team but waiting for the subject to contact the care team when the air leak has stopped. The subject will be followed until they have their chest tube removed.

3.2 Number of Subjects

560 subjects divided into two arms.

3.3 Duration of Participation

Subjects will participate in the study for 30 days following discharge from the hospital or until the chest tube has been removed if it remains in place more than 30 days post hospital discharge.



3.4 Primary Study Endpoints

Reduction in empyema in patient's discharging with an indwelling chest tube and valve.

3.5 Secondary Study Endpoints

Reduction of 30-day readmission in patient's discharging with an indwelling chest tube and valve.

3.6 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Patient Chest Tube Diary

The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (study source documents, electronic medical record):

- Laboratory results and clinical interpretation of the values
- Clinical significance of observations
- Hospital admissions

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- ≥ 18 years of age
- Male or Female
- Consultation with a thoracic surgeon
- Discharge from the hospital with a chest tube and valve in place
- Subject is able to understand the study procedures and provide informed consent.

4.2 Exclusion Criteria

- Pregnancy
- Allergy to cephalexin or clindamycin
- Special consideration should be taken in enrolling subjects with preexisting conditions that can be exacerbated by antibiotic use but are allowed at the discretion of the treating physician.

  Considerations include but are not limited to:

  - C. difficile
  - Colitis
  - Impaired renal function
  - Hypersensitivities to cephalosporins, penicillins, or lincomycin
  - Hepatic impairment
  - Anticoagulation therapy
  - Metformin usage
  - Probenecid usage

4.3 Subject Recruitment, Enrollment and Screening

A member of the research team will identify that a potential subject is going to be discharged from the hospital with a chest tube and valve in place. Once the subject's eligibility for the study has been determined the background of the proposed study and the benefits and risks of the study and procedures will be explained to the subject as a part of consenting process.

A signed, written informed consent document will be obtained from each subject by the investigator or his/her designee prior to the subject's involvement in the study. Routine clinical evaluations that would be performed as part of the normal clinical care of patients may be performed prior to such consent and used as part of the screening assessment. If the patient is subsequently consented and enrolled in the study, the results of such tests may be used as study data.

The process of obtaining informed consent will include the investigator or investigator's designee informing all subjects about:

- The expected duration and purpose of the study.
- The method of application and investigational nature of the device.

- The potential risks and benefits that may result from utilization of the device.
- The right to refuse participation in this clinical investigation and that if they should choose to participate, they may withdraw from the study at any time.

After consenting, subjects will be considered enrolled if they meet all the inclusion criteria and none of the exclusion criteria. Subjects who fail to meet any of the entry criteria will be excluded from the study and considered a screen failure. Screen failures will be recorded, and the reason(s) for exclusion will be documented.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any time. Additionally, a subject may also be discontinued from the study, if, based on the judgment of the Investigator, it is in the best medical interests of the subject. Withdrawal initiated by the patient may be documented by written or oral withdrawal of the original informed consent, or the implicit withdrawal of consent reflected in patient noncompliance or the patient being lost to follow-up.

Subjects are considered “lost to follow-up” after 3 attempts to contact the participant. Study coordinators will document all attempts to contact subjects.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Information collected before the participant withdraws consent can continue to be used; however, new information will not be collected.

5 Study Procedures

5.1 Visit 1

The subject will be identified for eligibility into the study. The study coordinator will consent and enroll the subject. For women of childbearing potential, a pregnancy test will be done if not done prior to surgery and it must be negative before you can continue in this study. Baseline data collected will include air leak status and surgical history.

5.2 Visit 2

Prior to their discharge from the hospital a member of the study team will review the instructions for completing the Patient Chest Tube Diary and will confirm that the standard clinical education for discharging with an indwelling chest tube and valve has been completed. For subjects randomized to Group 1 confirm that they have received their prescription for antibiotics. The antibiotic to be prescribed is cephalexin; it is the oral equivalent of the antibiotic used for perioperative coverage. In the event that the subject has an allergy to cephalexin or the cephalosporin group of antibiotics then clindamycin should be prescribed instead in following the typical perioperative coverage.

5.3 Daily Diary

The subjects will record daily in the Patient Chest Tube Diary or using the Medidata Patient Cloud App. Attachment 14.1.

5.4 Twice Weekly Telephone Calls (Group 1 Only)

The subjects in Group 1 will receive twice a week telephone calls from their coordinating medical team. Attachment 14.2.

5.5 Off Study

Subjects will be followed for 30 days following discharge from the hospital or until the chest tube has been removed if it remains in place for more than 30 days post hospital discharge. The patient will be instructed to return their Patient Chest Tube Diary at their next visit or via mail if they did not use the electronic app. A telephone call may be made in order to remind the participants to return their daily diary. Attachment 14.3.

Schedule of Events

Study Activity	Visit 1	Visit 2	Daily Diary	Twice Weekly Calls [a]	Off Study
Informed Consent	X				
Air Leak Status	X				
Surgical History	X				
Patient Education		X			
Patient Chest Tube Diary			X		
Telephone Assessment				X	
Adverse Event Evaluation			X	X	X

a: Group 1 only.

b: Includes microbiology assessment of infection if done as part of clinical care and data is available.

6 Statistical Plan

6.1 Sample Size Determination

A power analysis was done to determine the sample size. The differences in rates of empyema and 30-day readmission we explored using a two-sided test at an alpha-level of 0.05 and for 80% power. Rate reductions of 25%, 50% and 75% were evaluated. A reduction rate of 50% was selected for empyema and will require 253 patients in each arm for a total enrollment of 506 patients. In allowing an additional 10% for drop outs a total target enrollment of 560 patients will be needed. The 560 patients will give a rate reduction between 25% and 50% for 30-day readmission.

6.2 Statistical Methods

Descriptive Statistics

Descriptive statistics for baseline and clinical variables will be reported as number (percentage) for discrete variables and as mean (SD) or median (range) as appropriate for continuous variables. Baseline demographic and clinical variables will be reported by treatment group. These assessments will help identify potential confounding variables to be used as covariates in multiple variable models when examining the outcomes between treatment arms.

Handling of Missing Data

In the event that we have patients without complete follow-up survival analyses for the outcomes of 30 day empyema and 30 day readmission will be utilized to account for differential patient censoring.

Multiplicity

This study has two treatment arms being compared. No multiple comparison adjustments are planned.

Primary Hypothesis: Assess whether patients receiving antibiotics and twice weekly calls have reduced 30-day **empyema** rates post-discharge compared to patients on standard of care.

The primary analysis will be intention to treat (ITT). The proportion of patients having 30-day empyema in the two treatment arms will be estimated and reported along with a 95% confidence interval. The association of treatment arm with the rate will be assessed using a Chi square test. Additionally, logistic regression will be used to examine the treatment effect accounting for baseline covariates in which there is important imbalance between treatment arms. If not all patients having complete follow-up to 30 days post-discharge then these same analyses will be performed using survival methods, estimates of survival-free of empyema using Kaplan Meier methods and Cox models for the assessment of the association of treatment arm and the risk of empyema. The alpha level will be set at 0.05 for statistical significance.

Secondary Hypothesis 1: Assess whether patients receiving antibiotics and twice weekly calls have reduced 30-day **readmission** rates post-discharge compared to patients on standard of care.

The primary analysis will be intention to treat (ITT). The proportion of patients having a 30-day readmission in the two treatment arms will be estimated and reported along with a 95% confidence interval. The association of treatment arm with the rate will be assessed using a Chi square test. Additionally, logistic regression will be used to examine the treatment effect accounting for baseline covariates in which there is important imbalance between treatment arms. If not all patients having complete follow-up to 30 days post-discharge then these same analyses will be performed using survival methods, estimates of survival-free of readmission using Kaplan Meier methods and Cox models for the assessment of the association of treatment arm and the risk of readmission. The alpha level will be set at 0.05 for statistical significance.

6.3 Subject Population(s) for Analysis

The primary analysis will be intention to treat (ITT). A secondary analysis will be considered using a per protocol (PP) analysis.

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is defined as the time of consent until 30 days following hospital discharge or until the removal of the chest tube if after 30 days.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if it requires active management or treatment.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

7.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

Adverse event data related to the indwelling chest tube, valve, ongoing air leak, or antibiotic use (group one) occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

CTCAE Version 5.0 (v5.0: November 27, 2017) will be used to standardize classification and grading of Adverse Events.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log and notify the coordinating site. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

7.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

Information collected on the adverse event worksheet (and entered in the research database) will include:

- Subject's number
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research:
- If the adverse event was expected:
- The severity of the adverse event:
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

Relationship Index Example

The relationship of an AE to the study procedures is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study procedures; the event is clearly related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to the study procedures which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study procedures but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to the study procedures, unlikely to be attributed to concurrent disease or other drugs or chemicals.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the study procedures.

Severity Index
The maximum intensity of an AE should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

7.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.4.1 Data and Safety Monitoring Board

The Mayo Clinic Department of Surgery Data Safety and Monitoring Board (DSMB) will evaluate and adjudicate Serious Adverse Events and Specified Adverse Events as reported by the Investigators for relatedness to device and procedure. The DSMB will also be given the listings of all other adverse events (not Serious and not Specified) for review and to determine if additional adjudication is required. The DSMB will be given any information requested to adjudicate adverse events. The DSMB will meet twice yearly, or more or less often as needed.

7.4.2 Early Stopping Rules

The study will be paused temporarily until the DSMB can review if any patient is permanently disabled, has life threatening consequences (defined as Grade 4 adverse event by CTCAE Version 5.0), or dies in a manner that could be consistent with the antibiotic usage. The study will be continued if the event is demonstrably unrelated to subject's usage of antibiotics (for example, caused by indwelling chest tube or a surgical complication).

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management
Data will be entered into a Medidata RAVE database. Medidata RAVE is a secure, customizable Web application designed for collecting study data. Once collected, data can be automatically exported to Microsoft Excel or several common statistical software packages (SPSS, SAS, R and Stata) for analysis. Randomization will take place in the Balance module of Medidata RAVE and will be stratified by enrollment site.

Data Processing
Data will be entered by each research site. Data will be analyzed at the Mayo Clinic Rochester.

Data Security and Confidentiality
Medidata RAVE is a secure database which requires individual log on. Data from each site is only accessible by the site and the data managing site, Mayo Clinic Rochester.

Data Quality Assurance
Medidata RAVE has built in data checks. Source documents may be requested by the data management site, Mayo Clinic Rochester, in order to verify data if needed.

8.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717
   whichever is longer.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the individual obtaining the informed consent.

11 Study Finances

11.1 Funding Source

This study maintenance is financed through the Division of Thoracic Surgery Clinical Research Office at the Mayo Clinic Rochester.

12 Publication Plan

The Mayo Clinic and the study PI hold the primary responsibility for publication of the results of the study. The study will be registered with ClinicalTrials.gov prior to subject recruitment and enrollment, as well as posting of results to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

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14 Attachments

14.1 Patient Chest Tube Diary
14.2 Twice Weekly Telephone Script
14.3 Diary Return Telephone Script

14.1 *Patient Chest Tube Diary*

Group 1: Patient Chest Tube Diary

Protocol #: ___________ **Participant ID:** ______________________ **Physician:** _______________________

Instructions for you: This is a calendar for you to record information about your chest tube everyday.

If you have any questions, please contact: ____

Month:____________________________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
______	______	______	______	______	______	______
Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No	Did you take your antibiotic today? ☐ Yes ☐ No Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No
Comments:	Comments:	Comments:	Comments:	Comments:	Comments:	Comments:

Patient Signature ________________________________ Date______________

Study Coordinator Signature _________________________ Date______________

Date the chest tube was removed:

____

Group 2: Patient Chest Tube Diary

Protocol #: ___________ **Participant ID:** ______________________ **Physician:** _______________________

Instructions for you: This is a calendar for you to record information about your chest tube everyday.

If you have any questions, please contact: ____

Month:_____________________________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
_____	_____	_____	_____	_____	_____	_____
Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:	Does your chest tube have an air leak? ☐ Yes, looks differently than before ☐ Yes, looks the same as before ☐ No Comments:

Patient Signature ______________________________ Date_____________

Study Coordinator Signature __________________________Date_____________

Date the chest tube was removed:

____

14.2 *Twice Weekly Telephone Script*

Twice Weekly Telephone Script

Protocol Title: A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve
IRB #: 17-007774
Principal Investigator: Dr. K. Robert Shen

Introduction:

Hello, this is _____ calling from the Mayo Clinic in Rochester, Minnesota (if out of state). May I please speak to _____?

***If the participant is there continue with the script.

***If the participant is not there, ask when it would be a good time to speak with _____?

Describe the Reason for the Call:

We are calling to check in on the progress of your air leak and indwelling chest tube and valve. If you may recall you agreed to participate in A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve and you were randomized to the group which receives twice weekly telephone calls to follow up on your indwelling chest tube.

Does your indwelling chest tube with valve have an air leak?

- ☐ *No*
- ☐ *Yes*

  If yes, has the air leak changed?

  - ☐ *No*
  - ☐ *Yes*

    If yes, please explain:

Is there anything else we need to know about your indwelling chest tube and valve?

Closing

Thank you for participating in our research study. Please understand that your answers will remain confidential. Give them some follow-up contact information (name and telephone number) in case they think of any more questions afterwards.

14.3 *Diary Return Telephone Script*

Diary Return Telephone Script

Protocol Title: A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve
IRB #: 17-007774
Principal Investigator: Dr. K. Robert Shen

Introduction:

Hello, this is _____ calling from the Mayo Clinic in Rochester, Minnesota (if out of state). May I please speak to _____?

***If the participant is there continue with the script.

***If the participant is not there, ask when it would be a good time to speak with _____?

Describe the Reason for the Call:

As you may recall you agreed to participate in A Randomized Study Evaluating Patients Discharged with Indwelling Chest Tube and Valve and you were asked to complete a daily diary about your indwelling chest tube. We are calling to confirm that if your chest tube has been removed that you have returned your Patient Chest Tube Diary.

Has your chest tube been removed?

- *No*

  If no, as a reminder when it has been removed please note that on your diary and send it back in the provided envelope. If you do not have your envelope we would be happy to send one out to you.

- *Yes*

  If yes, have you returned your diary?

  - *No*

    If no, as a reminder please send it back in the provided envelope. If you do not have your envelope we would be happy to send one out to you.

  - *Yes*

    If yes, thank you so much for returning the diary.

Closing

Thank you for participating in our research study. Please understand that your answers will remain confidential. Give them some follow-up contact information (name and telephone number) in case they think of any more questions afterwards.