CLINICAL STUDY PROTOCOL

PROSPECTIVE EVALUATION OF CHEST TUBE SIZE AND MAXIMUM BARRIER PRECAUTIONS

Protocol Number: 04-17-06

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ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial

NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of this clinical trial have completed Human Subjects Protection and ICH GCP Training.
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Prospective Randomized Evaluation of 14F Thal Tube vs 28 French Chest Tube for Hemothorax and Use of Maximum Barrier Precautions
Phase:	Recruiting
Description of Sites/Facilities Enrolling Participants:	Carolinas Medical Center 1000 Blythe Blvd, Charlotte, NC 28203
Study Description:	Traumatic hemothorax and hemopneumothorax are common diagnoses which are typically treated by placement of a chest tube. A retrospective review has previously shown equivalence between 14 Fr chest tubes and 32 – 40 Fr chest tubes for the non-emergent drainage of hemothorax; however, this study was not randomized. We seek to perform a prospective randomized trial that is adequately powered comparing efficacy of 14 Fr thal tubes to 28 Fr chest tubes for non-emergent drainage of hemothorax and hemopneumothorax. Additionally, we will employ maximal barrier precautions for all chest tube insertions and compare empyema rates to our historical controls for patients with hemothorax, hemopneumothorax, and pneumothorax.
Study Population:	Patients aged 18 and older diagnosed with a traumatic pneumothorax, hemothorax or hemopneumothorax that require non-emergent placement of a thoracostomy tube as part of their care.
Aims:	**Aim 1:** Determine the safety and efficacy non-inferiority between small bore (14 Fr) and large bore (28 Fr) in the drainage of traumatic hemothorax and hemopneumothorax **Aim 2:** Determine the incidence of empyema in the setting of traumatic pneumothorax, hemothorax and hemopneumothorax with the addition of maximum barrier precautions [Time Frame: 90 days]
Study Hypothesis	**Aim 1:** The investigators hypothesize that there is non-inferiority in safety and efficacy between the different chest tube sizes **Aim 2**: Maximum barrier precautions associated with a decrease in empyema rate.

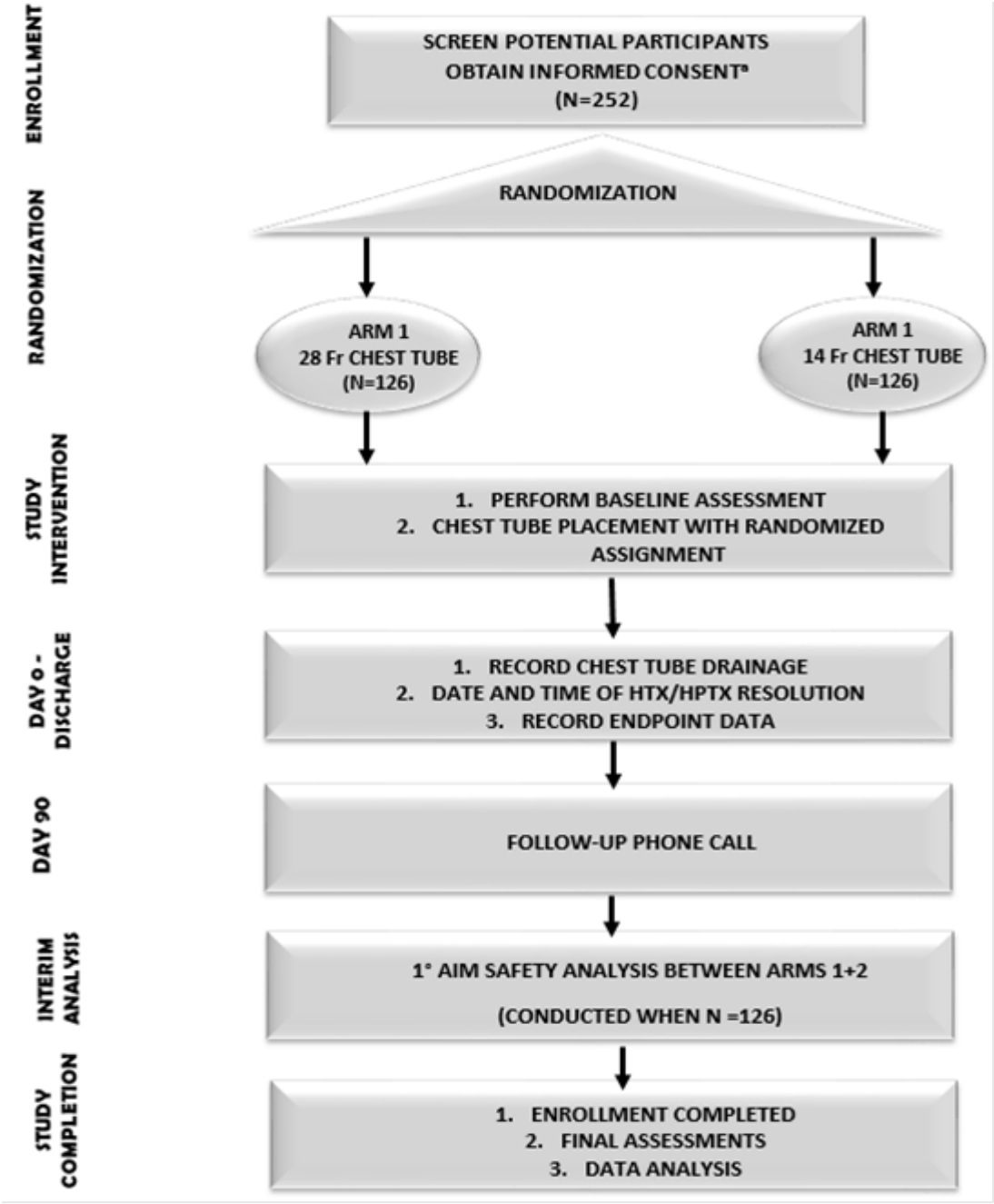
Number of Patients	**Aim 1:** With a sample size of n=126 per group, we will have 80% power to detect a non-inferiority margin difference between the group rates of 8% (allowing up to a 15% rate of drainage failure in the small 14 tube size group and approximately 7% in the large 28 tube size group; α=0.05). **Aim 2**: With assumptions of empyema rate is 5% in the retrospective group and 2% in the prospective group, 586 patients in each group are needed to achieve a power of 0.8 with α=0.05. To account for potential attrition, we will inflate the number of patients by 10% resulting in a total of 645 patients in the retrospective group and 645 patients in the prospective group.
Inclusion Criteria	1. The patient is admitted to the trauma service. 2. The patient has a pneumothorax, hemothorax and/or hemopneumothorax, requiring thoracostomy tube placement. 3. Thoracostomy tube placement is able to be performed or witnessed by an investigator listed on the study. 4. The patient has not had a chest tube in the past year. 5. The patient is $\geq$18 years of age. 6. In the event the patient is decisionally impaired, consent will be obtained from the individual's legally authorized representative (LAR) or from the individual's healthcare power of attorney (HPA). 7. In the instance of reversible impairment, initial consent would be obtained from the LAR/HPA and the patient will be approached for consent once he/she is deemed mentally competent by the care provider.
Exclusion Criteria	1. The patient is incarcerated 2. The patient is known to be pregnant 3. The patient is hemodynamically unstable, requiring emergent chest tube placement (in <10 minutes from evaluation). 4. The patient will have more than one chest tube placed at the time of enrollment.

Outcome measures	**Aim I** Primary outcome: • Retained hemothorax requiring an additional intervention, either video-assisted thoracoscopic surgery (VATS) or additional thoracostomy tube placement. Secondary outcome: • Duration of chest tube placement [Time Frame: 90 days] • Length of hospitalization • Subjective pain [Time Frame: 5 minutes pre- and post-insertion], Assessed with 0-10 numeric pain rating scale • Hemodynamic stability post-insertion (determined by vital signs: temperature, heart rate, blood pressure, oxygen saturation) • Initial drainage from chest tube at 5 minutes [Time Frame: 5 minutes] • Tube specific complications: Air leak, tube malposition, & tube migration [Time Frame: 90 days] • Time to radiographic resolution of pneumothorax/hemothorax/hemopneumothorax [Time Frame: 90 days] • Recurrent pneumothorax/hemothorax/hemopneumothorax after tube removal • Readmission for chest tube related complications [Time Frame: 90 days] **Aim II** • Empyema rates in traumatic pneumothorax, hemothorax, and hemopneumothorax
Description of Study Intervention:	Placement of 14 Fr Thal tube or 28 Fr Chest Tube for Hemopneumothorax.
Study Duration:	2 Years
Randomization	Permuted block randomization with random block sizes to allocate patients in a 1:1 allocation to the 14 or 28 tube sizes. The randomization lists will be generated using SAS Enterprise Guide version 6.1. All study staff collecting and recording data for the trial will be masked to the tube size that was used during the procedure.

Statistical Analysis	**Data Management:** All prospectively collected subject data will be recorded in Research Electronic Data Capture application (REDCap) software, collecting insertion specific data including use of a thyroid drape, use of hand scrubbing, gown, mask, sterile gloves, and surgical cap. The chest tube indication will be collected in the REDCap generated survey. The data will be entered into the electronic database within 3 business days of the enrollment or follow-up visit. **Statistical procedures for Analysis:** All analyses for this randomized trial will follow the intention to treat principle with an additional per protocol analysis given the non-inferiority hypothesis. We will first compare the baseline characteristics of the patients by group to assess for statistically significant or clinically meaningful imbalances. If either exists, these factors will be taken into account in sensitivity analyses for the primary and secondary outcomes. The rates of failure of drainage (primary outcome) will be estimated as proportions and compared between the two groups using a Chi-square test corrected for the non-inferiority hypothesis. We will present the findings using the difference in the proportions (rate in small group – rate in large group) and corresponding 95% upper confidence limit. Length of stay will be compared using Poisson regression with a main effect of group. Post insertion pain and vital signs will be compared using analysis of covariance controlling for pre-procedural pain and vital signs, respectively, with categorical group effect. We will compare rates of re-intervention and readmission using chi-square tests for independence (or Fisher's exact tests) and present our findings using relative risks and 95% confidence intervals. An interim analysis for inferiority will be conducted at 50% and 75% information accrual. This comparison of the primary outcome, failure of drainage, will be compared between the treatment arms with a one-sided test for superiority of the 28 tube compared to the 14 (α=0.05). There will be no missing data for the primary outcome as all information will be documented during surgery (no loss to follow up of the patient).

1.2 SCHEMA

Figure 1: Study Schema



[a] Patients who are GCS = 15 will be approached for consent prior to tube insertion. Patients who are GCS <15 will be approached (or their Legally Authorized Representative (LAR) will be approached) within 24 hours of insertion. If an LAR was used for initial consent, the patient will be consented if and when they become GCS = 15 within the follow up period of the study.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities

Study Requirement	Screening	Treatment Period		Follow Up
		Day 0	Day 1 – Discharge	Day 90
Eligibility Criteria	X			
Informed Consent[a]	X			
Demographics and Baseline Injury Characteristics	X			
Randomization		X		
Pain Scores	X	X		
Collect Barrier Precautions Data[b] & Antibiotic status		X		
Thoracostomy Tube Placement		X		
Vital Signs[c]	X (pre-placement)	X (post-placement)		
Hematologic, Chemistry and Coagulation Panel Labs	X			
Arterial Blood Gas Data (if applicable)	X			
Toxicology[d]	X			
Injury Severity Score	X			
Measurement of Chest Tube Drainage		→	→	→
Record Date & Time of PTX/HTX or HPTX Resolution[e]		→	→	

[a] Patients who are GCS = 15 will be approached for consent prior to tube insertion. Patients who are GCS <15 will be approached (or their Legally Authorized Representative (LAR) will be approached) within 24 hours of insertion. If an LAR was used for initial consent, the patient will be consented if and when they become GCS = 15 within the follow up period of the study.
[b] Barrier precautions recorded include hand hygiene, cap, gown, gloves, mask and thyroid drape
[c] Assessed 5 minutes before and after insertion of thoracostomy tube
[d] Serum and urine toxicology will be screened for ethanol, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana and opiates only if it is done as standard of care treatment for that patient.
[e] Radiologist-confirmed resolution of pneumothorax (PTX), hemothorax (HTX) and hemopneumothorax (HPTX)

Study Requirement	Screening	Treatment Period		Follow Up
		Day 0	Day 1 – Discharge	Day 90
Collect Data on Thoracostomy Tube Misplacement, Air Leak, & Migration		→	→	→
Collect Data on Additional Thoracostomy Tubes		→	→	→
Assess for Empyema and Fibrothorax		→	→	→
Collect Operative Interventions data[f]		→	→	→
Record Critical Care and Hospital Stay Parameters[g]				X
Survival				X
Hospital Readmissions				X
Adverse Events/ Serious Adverse Events		→	→	→

[f]Refers to video-assisted thoracoscopic surgery (VATS), thoracotomy or thoracostomy tube replacement
[g]Hospital length of stay (days), ICU stay (days), Mechanical ventilation days

2 INTRODUCTION

2.1 BACKGROUND

Trauma is the leading cause of death for Americans ages 1-44 and a major cause of morbidity and mortality worldwide.[1] Tube thoracostomy for drainage of blood and/or air in the thoracic cavity is a common procedure for patients sustaining both blunt and penetrating thoracic trauma. Within the last ten years, smaller bore chest tubes (≤20 Fr) are being used with increasing frequency to treat these patients.[2] Increasing evidence continues to show less pain and similar efficacy of the small-bore tubes[3,4]. Presently, size 14 Fr catheters are routinely used for pneumothorax and occasionally used for hemothorax. Kulvatunyou et al demonstrated no difference in efficacy between small and large bore (>20 Fr) chest tube size for the treatment of hemothorax. However, the study sample was small and usage of the small-bore catheters was selective. Data regarding complications of tube placement and removal, duration of thoracostomy placement, and complications from different tube sizes particularly in the setting of hemothorax is still lacking [3,4].

Catheter related bloodstream infections have been successfully reduced using a bundle including maximal barrier precautions[6]. Literature regarding empyema rates and the use of maximum barrier precautions during thoracostomy tube insertion remains scarce. A well designed prospective study has yet to be developed to properly address the chest tube size in the setting of traumatic hemothorax/hemopneumothorax or empyema rates with the use of maximum barrier precautions

2.2 STUDY RATIONALE

Currently, there are no specific guidelines regarding the optimal chest tube size for the treatment of traumatic hemothorax or hemopneumothorax. The efficacy and safety of large bore tubes for pleural drainage is well documented and is considered standard practice[7]. While a randomized study comparing small vs. large bore chest tubes for pneumothorax has been performed the sample size was small and hemothorax was excluded[8]. The investigators have designed a large randomized clinical trial to address the limitations of the data regarding thoracostomy tube size in the treatment of traumatic hemothorax and hemopneumothorax. The investigators hypothesize that there is safety and efficacy non-inferiority between the different chest tube sizes (Aim 1).

In our previous retrospective study, we saw a decrease in empyema rates with 14 Fr catheters (small bore) for pneumothorax where the use of a large drape is standard of care for barrier protection. This prospective study, also seeks to determine the efficacy of the addition of maximal barrier precautions in the prevention of empyema for patients with hemothorax and/or pneumothorax (Aim 2).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Some risks from the insertion procedure are:

- Bleeding or infection where the tube is inserted
- Improper placement of the tube (into the tissues, abdomen, or too far in the chest)
- Injury to the lung
- Injury to organs near the tube, such as the spleen, liver, stomach, heart, or diaphragm
- Infection

2.3.2 KNOWN POTENTIAL BENEFITS

- Drainage of blood, fluid, or air from around lungs, heart, or esophagus.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Those patients randomized to 14 Fr. Chest tube insertion may experience less pain, but also may be subject to a higher retained hemothorax rate. No additional risks are being subjected to the patient as tube thoracostomy is standard of care and both devices are FDA approved for drainage of fluid.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
	Primary
Aim I: Determine the safety and efficacy non-inferiority between small bore (14 Fr) and large bore (28 Fr) in the drainage of traumatic hemothorax and hemopneumothorax	**Endpoint I:** Retained hemothorax requiring an additional intervention, either video-assisted thoracoscopic surgery (VATS) or additional thoracostomy tube placement.
	Secondary
	Endpoint II: Duration of chest tube placement
	Endpoint III: Initial drainage from chest tube at 5 minutes
	Endpoint IV: Length of hospitalization
	Endpoint V: Subjective pain score (pre- and post-insertion recorded within 5 minutes of insertion). Assessed with 0 -10 numerical pain scale
	Endpoint VI: Hemodynamic stability post-insertion (determined by vital signs: temperature, heart rate, blood pressure, oxygen saturation)
	Endpoint VII: Time to radiographic resolution of pneumothorax, hemothorax, hemopneumothorax
	Endpoint VIII: Tube specific complications: Air leak, tube malposition, & tube migration
	Endpoint IX: Recurrent pneumothorax/hemothorax/hemopneumothorax after tube removal
	Endpoint X: Readmission to hospital for a chest tube related complication

OBJECTIVES	ENDPOINTS
Aim II: Determine the incidence of empyema in the setting of traumatic pneumothorax, hemothorax, and hemopneumothorax with the addition of maximum barrier precautions	**Endpoint Ia:** Empyema rate

4 STUDY DESIGN

4.1 OVERALL DESIGN

The proposed study is a single center, prospective, non-inferiority trial evaluating the efficacy of small bore (14 Fr) vs large bore thoracostomy tubes in the setting of trauma at an American College of Surgeons designated Level I trauma center. Each patient will receive a study approved thoracostomy tube as indicated and our standard of care thoracostomy tube Practice Guideline will be followed. The study period is from the time of enrollment (visit day 0) up to 90 days (±14 days) following the date of thoracostomy tube placement. A total of 645 subjects will be prospectively enrolled.

Aim I will be achieved through a prospective randomized study design which will evaluate thoracostomy tubes placed in the setting of traumatic hemothorax or hemopneumothorax. The efficacy of the thoracostomy tube sizes will be determined by assessing the participants for retained hemothorax which will be define in this study as any residual blood that cannot be drained after 72 hours of thoracostomy as confirmed by imaging. A total of 252 subjects will be enrolled and randomized in this study group.

Aim II will be achieved through a prospective non-randomized controlled study design in which maximum barrier precautions will be used during chest tube placement for all prospective subjects diagnosed with a traumatic pneumothorax, hemothorax or hemopneumothorax. The prospective subjects will be compared to subjects in a retrospective analysis in which the use of maximum barrier precautions was not standard. Maximal barrier precautions will consist of a thyroid drape, hand hygiene, sterile gown, mask, and gloves. The use of sterile technique will be consistent throughout the prospective study. This will limit the variability between the two treatment arms and allow a more accurate comparison of empyema rates between tube size and sterile technique. The use of prophylactic antimicrobial agents will also be collected for these subjects. A total of 645 subjects will be enrolled in this study group (inclusive of those patients enrolled as part of Aim I).

All participants will be monitored for their need for operative intervention (e.g. VATS), development of empyema, hospital readmission, tube related complications (e.g. tube misplacement, tube migration), and death which occurs between thoracostomy tube placement and follow-up.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

There is currently not enough evidence in the literature to know which size chest tube is best in this patient population, which is a primary purpose of the study.

4.3 END OF STUDY DEFINITION

The study will be complete once target enrollment has been achieved and all outcomes information is available.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- The patient is admitted to the trauma service.
- The patient has a hemothorax and/or or hemopneumothorax, requiring thoracostomy tube placement.
- Thoracostomy tube placement is able to be performed or witnessed by an investigator listed on the study.
- The patient has not had a chest tube in the past year.
- The patient is ≥18 years of age.
- In the event the patient is decisionally impaired, consent will be obtained from the individual's legally authorized representative (LAR) or from the individual's healthcare power of attorney (HPA).
- In the instance of reversible impairment, initial consent would be obtained from the LAR/HPA and the patient will be approached for consent once he/she is deemed mentally competent by the care provider.

5.2 EXCLUSION CRITERIA

- The patient is incarcerated
- The patient is known to be pregnant
- The patient is hemodynamically unstable, requiring emergent chest tube placement (in <10 minutes from evaluation).
- The patient will have more than one chest tube placed at the time of enrollment.

5.3 SCREEN FAILURES

Screen failure patients for this study are those who choose to withdraw from the study or who are discovered to meet exclusion criteria after enrollment.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Subject enrollment will take place at a single American College of Surgeons designated Level I trauma center. A partial waiver of authorization will be requested for the purposes of pre-screening for enrollment via electronic medical record review. All patients 18 years of age and older sustaining trauma that requires therapeutic tube thoracostomy will be screened for study eligibility by the research staff. Participants will be approached for consent as soon as it has been determined that the patient has met all inclusion criteria and no exclusion criteria.

The study design aims to maintain high patient retention throughout the study period. Subject retention strategies include limiting study involvement to three months and limiting subject follow-up to electronic medical record review supplemented by a single telephone call.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

Screened subjects eligible for study participation will have their inclusion/exclusion criteria verified by an investigator. The subject will be approached for consent by the research staff and enrolled. Subjects with suspected pneumothorax alone will receive either a small bore (14 Fr) or large bore (28 Fr) tube chosen based on physician preference. Subjects with suspected hemothorax or hemopneumothorax will be randomized to receive either a small or large bore chest tube.

Enrolled subjects will have their thoracostomy tube placement procedure observed and verified by an investigator listed on this protocol. The training level of the individual performing the procedure will be recorded. Maximum barrier precautions for this study will be used during the placement procedure for all prospective subjects. Maximum barrier precautions for this study will be defined as the correct use of proper hand hygiene, a cap, surgical gown, sterile gloves, mask, and a thyroid drape. The institutional standard of care thoracostomy tube Practice Guidelines will be followed.

6.2 INDEX HOSPITALIZATION REVIEW

At the time of enrollment, baseline demographic and injury characteristics will be recorded. Baseline data to be recorded include:

- Demographics (age, sex)
- Vital signs (pre- and post-tube insertion)
- Mechanism of injury (blunt vs penetrating)
- Radiographic findings (pneumothorax, hemothorax or hemopneumothorax)
- Initial laboratory values (hematologic panel, chemistry panel, coagulation panel, toxicology, blood gases)
- Calculated injury severity score

The day of tube insertion will mark study day 0. Subjects will be monitored daily by study staff in the form of chart review for the duration of their hospitalization. A daily data log will be kept for each patient/ The information to be recorded includes:

- Volume of hemo/hemopneumothorax drainage
- Tube misplacement
- Tube migration
- Presence of air leak
- Need for additional thoracostomy tubes

- Need for operative intervention (VATS, thoracotomy)
- Date and time of pneumo/hemo/hemopneumothorax resolution as confirmed by a radiologist
- Date and time of chest tube removal
- Recurrent pnemo/hemo/hemopneumothorax
- Development of infection

6.3 THREE (3) MONTH FOLLOW-UP (DAY 90±14)

Each participant will be followed for three months (90 days). Participants will receive a telephone follow-up on day 90 (+/-2 weeks). Information obtained during the call will include: survival, adverse events and readmission to any hospital for complications related to chest tube placement (e.g. empyema, re-accumulation/recurrent pneumo- or hemothorax, fibrothorax).

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

We will use stratified permuted block randomization with random block sizes to allocate patients in a 1:1 allocation to the 14 or 28 tube sizes. The randomization lists will be generated by a study statistician using SAS Enterprise Guide version 6.1 and stratified by location (Emergency Department and Surgical & Trauma ICU). Randomization lists will be provided to the study coordinator and another study team member not affiliated with clinical care and assessments to place the allocations into number opaque envelopes. These envelopes will be pulled sequentially by the surgeon or study team as a patient is deemed provisionally eligible for the study preserving allocation concealment. The ID of the envelope is recorded in the patient's research record.

6.5 CONCOMITANT THERAPY

All concomitant medications and interventions are permissible during the study. Data on concomitant antimicrobial therapy administered at the time of thoracostomy tube placement will be collected. Antimicrobial agents include antibacterial, antiviral, antifungal, and anti-parasitic medications.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If the initial thoracostomy tube has inadequate drainage, the primary care team reserves the right to replace the tube. The patient will not be removed from the study and this data will be collected as an outcome.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants will be informed at the time of consent that they are free to withdraw from the study at any time and for any reason. They will be assured that their medical care will not be affected should they elect to discontinue participation in the study. The date the patient has withdrawn from the study will be recorded.

7.3 LOST TO FOLLOW-UP

At Day 90 a telephone call will be made to the participant to assess outcome. Three attempts will be made to establish contact. If contact is not achieved, the electronic medical record will be the only source used to complete the data set.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The rates of failure of drainage (primary outcome) will be estimated as proportions and compared between the two groups using a Chi-square test corrected for the non-inferiority hypothesis. The margin of non-inferiority is defined as of 8%.

8.2 SAFETY AND OTHER ASSESSMENTS

The PI and the study team will meet biweekly to review the study procedures, enrollment (screening and randomization), implementation, protocol deviations, data collection, and adverse events. The biostatistics team will generate monthly reports for the study team which will monitor screening, enrollment, completeness of data for intervention implementation and outcomes, adverse events, and protocol deviations.

A medical monitor will determine the course of action necessary to meet safety goals and objectives. After the first 20 patients are enrolled and randomized, the study statisticians will generate a safety report for medical monitor review. An interim analysis for inferiority at 50% and 75% information accrual (see section 9.4.4: Planned Interim Analysis) will also be conducted. The medical monitor will recommend stopping if there is an increased incidence of procedure related serious complications or deaths in either treatment group that is found to be clinically significant.

Safety endpoints assessed by the study team and medical monitor will include:

- General safety assessments
    - Incidence of unanticipated serious adverse events related to chest tube size
- Thoracostomy tube related safety events
    - Hemodynamic instability post-insertion
    - Need for additional interventions (VATS, thoracotomy, chest tube replacement)
    - Procedure related deaths
    - Empyema
    - Re-accumulation/Recurrent pneumo- or hemothorax
    - Readmission to hospital within 90 days of insertion

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject temporally associated with the use of a medical treatment or procedure that may or may not be related to the use of the medical treatment or procedures.

In this study, we will not be recording AEs unrelated to thoracostomy tube size, as both of the thoracostomy tubes used in this study are being used within their approved indications.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., treatment, follow-up), that results in one or more of the following:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

In this study, we will only be reporting SAEs that are determined to be unexpected and possibly, probably, or definitely related to the size of the initial thoracostomy tube. The principal investigator will assess all potential adverse events for this criteria.

SAEs will be reported in the manner and timeframe that is outlined in the Chesapeake IRB handbook.

8.3.3 SEVERITY OF EVENT

The Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 developed by the National Institutes of Health's National Cancer Institute will be used as a severity scale for each AE and SAE. The general descriptions of severity for each adverse event is as follows:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

8.3.4 RELATIONSHIP TO STUDY INTERVENTION

The principle investigator will assess the relationship of an adverse event to the thoracostomy tube insertion procedure or tube size will be the according to the following definitions:

Unrelated	There is no evidence of any causal relationship
Possibly related	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event.
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

8.3.5 EXPECTEDNESS

The principle investigator is responsible for assessing the expectedness of an event. Expected safety events of interest for this study include: misplacement of tube, tube migration, death during insertion procedure, air leak, empyema, need for additional interventions (VATS, thoracotomy, chest tube replacement), catheter related blood stream infection and thoracostomy tube related hospital readmission. For the purposes of this study, deaths will be captured as clinical outcomes and do not need to be reported as SAEs unless determined by the principle investigator to be related to chest tube size.

All unanticipated problems that meet study definition will be reported to the IRB. An unanticipated problem is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence

in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21CFR 812.3(s)).

8.3.6 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Participants will be assessed for AEs and SAEs daily during hospitalization and at 90-day follow-up.

8.3.7 SERIOUS ADVERSE EVENT REPORTING

Participants will be monitored for serious adverse events from the moment of randomization through 90 days post tube insertion. Due to their mechanism of injury and high trauma burden, participants are expected to have significant trauma related complications. AEs or SAEs determined to be unrelated to study procedure or tube size will not be reported to the IRB. Submission of any serious adverse event will not occur until relatedness of the event has been determined.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):

- Aim I
  - Retained hemothorax requiring an additional intervention, either video-assisted thoracoscopic surgery (VATS) or additional thoracostomy tube placement.
- Aim II
  - Empyema rates in traumatic pneumothorax, hemothorax, and hemopneumothorax

Secondary Efficacy Endpoint(s):

- Aim I
  - Duration of chest tube placement
  - Initial drainage from chest tube at 5 minutes
  - Length of hospitalization
  - Subjective pain score (pre- and post-insertion recorded within 5 minutes of insertion). Assessed with 0 -10 numerical pain scale
  - Hemodynamic stability post-insertion (determined by vital signs: temperature, heart rate, blood pressure, oxygen saturation)
  - Time to radiographic resolution of pneumothorax, hemothorax, hemopneumothorax
  - Tube specific complications: Air leak, tube malposition, & tube migration
  - Recurrent pneumothorax/hemothorax/hemopneumothorax after tube removal
  - Readmission to hospital for a chest tube related complication

9.2 SAMPLE SIZE DETERMINATION

Aim I

This study is a non-inferiority randomized controlled trial comparing placement of 14 French vs. 28 French chest tubes for hemothorax and hemopneumothorax. We hypothesize the rate of drainage failure to be approximately 7% in the large 28 tube size group. With a sample size of n=126 per group, we will have 80% power to detect a non-inferiority margin difference between the group rates of 8% (allowing up to a 15% rate of drainage failure in the small 14 tube size group; α=0.05). In our prior study, we saw a 20% vs 6.7% difference in needing additional procedures for pneumothorax with small vs large catheters but these numbers are based on draining air not blood. Sample size analyses were conducted in PASS 13[9].

Aim II

Calculations of sample size were based on two-group comparisons of empyema rates. With assumptions of empyema rate is 5% in the retrospective group and 2% in the prospective group, 586 patients in each group are needed to achieve a power of 0.8 with α=0.05. To account for potential attrition, we will inflate the number of patients by 10% resulting in a total of 645 patients in the retrospective group and 645 patients in the prospective group. The sample size was calculated by using the PASS 15[10].

9.3 POPULATIONS FOR ANALYSES

The study population will consist of patients aged 18 and older diagnosed with a traumatic pneumothorax, hemothorax or hemopneumothorax that require non-emergent placement of a thoracostomy tube as part of their care.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All analyses for this randomized trial will follow the intention to treat principle with an additional per protocol analysis given the non-inferiority hypothesis. We will first compare the baseline characteristics of the patients by group to assess for statistically significant or clinically meaningful imbalances. If either exists, these factors will be taken into account in sensitivity analyses for the primary and secondary outcomes.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The rates of failure of drainage (primary outcome) will be estimated as proportions and compared between the two groups using a Chi-square test corrected for the non-inferiority hypothesis. We will present the findings using the difference in the proportions (rate in small group –rate in large group) and corresponding 95% upper confidence limit.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Length of stay will be compared using Poisson regression with a main effect of group. Post insertion pain and vital signs will be compared using analysis of covariance controlling for pre-procedural pain and vital signs, respectively, with categorical group effect. We will compare rates of re-intervention and readmission using chi-square tests for independence (or Fisher's exact tests) and present our findings using relative risks and 95% confidence intervals.

9.4.4 PLANNED INTERIM ANALYSES

An interim analysis for inferiority will be conducted at 50% and 75% information accrual. This comparison of the primary outcome, failure of drainage, will be compared between the treatment arms with a one-sided test for superiority of the 28 tube compared to the 14 (α=0.05).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The IRB approved informed consent form (ICF) will adhere to ICH GCP guidelines and comply with the United States Code of Federal Regulations as detailed in 21 CFR §50.25 and the Declaration of Helsinki.

Once eligibility has been confirmed, an investigator/research coordinator will approach each patient or legally authorized representative (LAR) to explain the nature of the study, its purpose, expected duration, alternative forms of therapy available, benefits and risks of study participation. Patients who are GCS = 15 will be approached prior to thoracostomy tube insertion for study consent. Patients with GCS <15 will either be consented by LAR or approached for self-consent if mentation normalizes within 24 hours of tube insertion. Where consent has been obtained from a LAR; the patient will be approached for consent if the investigator later deems the patient GCS = 15 during the study period.

It is expected that most patients/ LARs will be approached in either the emergency room or intensive care unit for consent. After this explanation and before enrollment, the patient or authorized legal representative will be given ample time and opportunity to read the consent form. Patients/LARs who choose to participate will voluntarily sign and date the form in the presence of the investigator/research coordinator.

It will be pointed out to the patient/LAR that they can refuse to participate in the study or withdraw from the study at any time without prejudice to further care and treatment.

The patient/LAR will be given a copy of the signed and dated informed consent form. The acquisition of informed consent will be documented in the patient's medical records.

Patients/LARs will be informed of any significant new finding which arises during the course of study participation that may affect their decision to continue participation.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The investigator reserves the right to terminate the study at any time. Should this be necessary, the investigator will notify the appropriate regulatory authority (ies), and IRB. In terminating the study, the investigator will assure that consideration is given to protect the interests of the patients.

10.1.3 CONFIDENTIALITY AND PRIVACY

The investigator assures that patients' anonymity will be strictly maintained and that their identities will be protected from unauthorized parties. The Investigator will keep a patient identification log showing codes, names, ages and sex for all patients screened and enrolled in the study. Identifying patient information will not be shared with parties not part of the research team.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principle Investigator- The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH GCP guidelines, the Declaration of Helsinki and applicable institutional regulatory requirements.

Medical Monitor (MM)- The MM will provide medical guidance and oversee the safety aspects of the study. The MM is responsible for monitoring serious adverse events (SAEs) on an ongoing basis to ensure participant safety.

Quality Assessment Nurse - The quality assessment nurse will review patient enrollment weekly and provide a secondary point of review to monitor patients for significant chest tube related complications (e.g. ICU re-admissions, hospital re-admissions, re-current pneumothoraces/hemothoraces, etc.). All complications reported by the patient or staff will be reported to the quality assessment nurse.

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Subject data will be collected and entered by authorized research staff in the Research Electronic Data Capture application (REDCap) system which is compliant with 21 CFR Part 11. This is a secure, web-based system, allowing those with permission to access data from any location at any time. The electronic case report forms generated will create a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

10.1.6.2 STUDY RECORDS RETENTION

Paper records for the study will be maintained for a minimum of 3 years after study. All paper records will be will be stored in a central location with restricted access in locked file cabinets. Access will only be granted to designated research staff.

10.1.7 PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol except for emergency situations in which the protection, safety and wellbeing of the patient requires immediate intervention based upon the judgement of the investigator. Protocol deviations will be recorded with an explanation as well as actions that were taken to mitigate their effects. Deviations that impact the rights, welfare or safety of patients shall promptly be reported to the IRB as required.

10.1.8 CONFLICT OF INTEREST POLICY

This is an internally funded clinical trial. None of the investigators have received or will receive money or other benefits for personal use from this study.

11 REFERENCES

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10 PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass

12 APPENDICES

12.1 APPENDIX A: TRAUMA PRACTICE GUIDELINE

Diagnostic Evaluation **Phase:** **Tube Thoracostomy Management and Simple Pneumothorax**	Last reviewed/revised: July 2016

This guideline is a suggested approach and is intended to supplement rather than substitute, for professional judgment. The care provider may change this plan depending upon clinical circumstances and available resources, but should clearly document in the medical record the rationale for doing so. Failure to comply with this pathway does not represent a breach of the standard of care.

I. Purpose: To have a guideline for tube thoracostomy management and simple pneumothorax management.
II. The indications for the placement of a chest tube include:
    a. Hemothorax or pneumothorax by CXR or CT scan.
    b. Prophylactic chest drainage in patients with severe blunt chest trauma requiring positive pressure ventilation.
    c. Clinically significant pleural effusions or other pleural collections.
    d. Evidence of subcutaneous air in chest and/or neck.
III. Chest tube insertion
    a. A 14 F catheter may be used as first line treatment. A large bore catheter (28F or greater) may be used according to physician judgment.
IV. Chest Radiographs
    a. Post insertion CXR for tube placement should be done routinely after insertion.
    b. A routine CXR (PA/Lateral) should be obtained after the chest tube has been removed. ANY development of respiratory distress or evidence of patient deterioration warrants an immediate STAT CXR.
    c. When placing the patient on water seal from suction, a routine CXR is not necessary.
    d. Consideration should be given for obtaining a CXR when placing to water seal for any patient who has had a recurrent residual pneumothorax.
V. An abrupt decrease in chest tube output (>50% decrease compared to prior 24 hours output) may indicate that the chest tube is no longer functional. Consider obtaining CXR to rule out significant re-accumulation of pleural fluid before discontinuing chest tube.
VI. References
    a. BET 4: Does size matter? Chest drains in hemothorax following trauma: Table 4. Emergency Medicine Journal. 2013;30(11):965-967.

b. Kulvatunyou N, Erickson L, Vijayasekaran A, Gries L, Joseph B, Friese R et al. Randomized clinical trial of pigtail catheter versus chest tube in injured patients with uncomplicated traumatic pneumothorax. British Journal of Surgery. 2013;101(2):17-22.

VII. Algorithms