Interventional Radiology vs. ERC for Perihilar Biliary Tumors: The INTERCPT Trial

A Multicenter Randomized Trial of Percutaneous Transhepatic Biliary Drainage vs. Endoscopic Retrograde Cholangiography for Decompression of Suspected Malignant Biliary Hilar Obstruction

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Investigators' Agreement

I have read the attached clinical protocol titled "A Multicenter Randomized Trial of Percutaneous Transhepatic Biliary Drainage vs. Endoscopic Retrograde Cholangiography for Decompression of Suspected Malignant Biliary Hilar Obstruction" revised in April, 2018 and agree to conduct the protocol as written in this document.

I agree to comply with the Declaration of Helsinki/Tokyo/Venice on Experimentation in Humans as required by the United States Food and Drug Administration regulations, Code of Federal Regulations parts 50, 56, 312, ICH Good Clinical Practice Guidelines and all other applicable guidelines.

I understand this document contains confidential information of the Department of Gastroenterology and Hepatology at the Medical University of South Carolina and cannot be disclosed to anyone other than study team members and members of the Institutional Review Board or Ethical Committee.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of this clinical trial without the prior written permission of the Study Chairpersons.

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Signature of Principal Investigator Date

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Printed name of Principal Investigator

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Signature of Co-Principal Investigator (When applicable) Date

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Printed name of Co-Principal Investigator (When applicable)

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1.0 SUMMARY

Protocol Title	Interventional Radiology vs. ERC for Perihilar Biliary Tumors
Acronym	INTERCPT
Clinical Trial Phase	Phase III
Study Sites	Approximately twenty-five clinical centers in the United States
Study Period	Planned enrollment period – 2.5 years Planned duration of the study – 4 years
Study Population	Patients with cholestasis due to suspected malignant hilar obstruction (MHO) who are candidates for percutaneous transhepatic biliary drainage (PTBD) and endoscopic retrograde cholangiopancreatography (ERC).
Primary Study Objective	To compare the effectiveness of PTBD vs. ERC in achieving **successful biliary drainage** in patients with MHO.
Secondary Study Objectives	To compare adverse events, resource utilization, and diagnostic capacity between the PTBD first and ERC first groups.
Study Design	A comparative effectiveness, multi-center, randomized superiority trial of PTBD vs. ERC for decompression of suspected MHO.
Sample Size	A maximum sample size of 184 subjects (92 in each arm) will be needed for a two-sided significance level of 0.05 and 85% power to detect a 20% difference in the rate of successful biliary drainage between groups, assuming a rate of 90% in the PTBD group and 70% in the ERC group.
Inclusion Criteria	Any patient with cholestasis due to suspected MHO, who provides written informed consent, AND: Has **all three** of the following: (1) Age ≥40 (to reduce the likelihood of enrolling patients with obstruction due to primary sclerosing cholangitis) (2) Cholestatic liver function tests, including serum alkaline phosphatase level ≥ 300 IU/L and bilirubin level ≥ 3.7 mg/dL

	(3) Radiographic evidence of a biliary hilar stricture *OR* intrahepatic *but no extrahepatic* biliary ductal dilation
Exclusion Criteria	1) Known radiographic evidence of a Bismuth-Corlette type 1 biliary stricture (2) Known diagnosis of primary sclerosing cholangitis *without* suspicion of dominant hilar stricture (3) Recent cholecystectomy, liver resection, or biliary surgery within 12 months (4) Known Mirizzi syndrome (5) Known IgG4-mediated cholangiopathy (6) Significant liver metastatic disease interfering with safe/effective PTBD (7) Significant peri-hepatic ascites interfering with safe/effective PTBD (8) Known UGI tract obstruction precluding ERC (9) Known regional malignant-appearing adenopathy or extra-biliary mass, indicating the need for concurrent EUS-FNA (10) Prior ERCP or PTBD for hilar obstruction (11) Surgically altered luminal anatomy other than prior Billroth reconstruction. (12) Standard general contraindications to ERCP or PTBD (e.g. hemodynamic instability, uncorrected coagulopathy) (13) Pregnancy (14) Inability or unwillingness to follow study protocol
Study Intervention and Follow-up	Eligible patients who provide written informed consent will be randomized to PTBD or ERC first. All clinical interventions after randomization will be deferred to treating physicians per usual care. Subjects will be followed for 6 months after randomization.
Primary Outcome Measure	***Successful biliary drainage***, defined as a 50% reduction from baseline in bilirubin level within 3 weeks after the study intervention without additional ERC or PTBD during that timeframe.

Statistical Analysis for Primary Outcome Measure	For analysis of the primary endpoint, we will use a chi-squared or Fisher's exact test to compare the proportion of participants achieving successful biliary drainage in the PTBD vs. ERC groups, with two-sided $p < 0.05$ indicating statistical significance.

1.1 Acronyms

DSMB – Data and Safety Monitoring Board
DSMP – Data and Safety Monitoring Plan
ERC – Endoscopic Retrograde Cholangiography
EUS – Endoscopic Ultrasound
FDA – Food and Drug Administration
GCP – Good Clinical Practice
GI – gastroenterology
ICH – International Conference on Harmonisation
IR – interventional radiology
IRB – Institutional Review Board
MHO – Malignant Hilar Obstruction
MoP – Manual of Procedures
MUSC – Medical University of South Carolina
PEP – Post-ERCP Pancreatitis
PI – Principal Investigator
PTBD – Percutaneous Transhepatic Biliary Drainage
RCT – Randomized Controlled Trial
SAE – Serious Adverse Event
SC – Steering Committee
SDMC – Statistical & Data Management Center
SSL – Secure Socket Layer

2.0 OBJECTIVES

2.1 Primary

To compare the effectiveness of PTBD vs. ERC as the first intervention in achieving successful biliary drainage among patients with MHO.

2.2 Secondary

1. To compare adverse events, procedural requirements, and hospitalizations in the PTBD vs. ERC-first strategies.

2. To compare the rates of adequate tissue diagnosis of suspected MHO during the index PTBD vs. the index ERC.

3.0 BACKGROUND AND RATIONALE

3.1 Background

To date, no randomized trials comparing percutaneous transhepatic biliary drainage (PTBD) to endoscopic retrograde cholangiography (ERC) for decompression of suspected malignant hilar obstruction (MHO) have been published. In routine clinical practice, ERC is favored on the basis of: 1) high technical and clinical success rates of ERC for other (non-MHO) indications; 2) the perceived safety of ERC relative to PTBD; 3) the perceived ability to perform more comprehensive tissue sampling at the time of ERC compared to PTBD; 4) the avoidance of external tubes which are often needed for PTBD; and 5) because patients with MHO typically present to and are managed by gastroenterologists. However: 1) observational data suggest that PTBD is superior for achieving complete drainage of MHO[1] and some guidelines recommend the percutaneous approach over ERC for Bismuth type 3 & 4 hilar strictures[2]; 2) the generally quoted risks of PTBD are based on outdated studies and may be exaggerated; 3) endoscopic diagnosis of indeterminate biliary strictures remains suboptimal despite the use of cholangioscopy and multi-modal sampling; and 4) we and others have observed that many patients who undergo initial ERC require subsequent PTBD for adequate drainage.

3.2 Rationale

Thus it remains unclear whether ERC or PTBD should be offered first for the decompression of patients with cholestasis due to suspected malignant biliary hilar obstruction. We hypothesize that even though PTBD will be more effective than ERC for drainage of suspected MHO, this advantage will be offset by the favorable safety profile and superior diagnostic capability of ERC. If, however, PTBD is found to be substantially superior in terms of drainage, or if the potential advantages of ERC are not realized, then the existing clinical approach to MHO must be reappraised. Moreover, identifying patient and stricture characteristics that predict response to PTBD or ERC may be important for informing clinical decision-making and guidelines.

4.0 STUDY PLAN

4.1 Study Design

A multi-center comparative effectiveness, randomized superiority trial of PTBD vs. ERC for decompression of suspected MHO.

4.2 Study Sites

The study will be conducted at approximately twenty tertiary care academic medical centers in the United States. Each study center will have a site PI who is responsible for the overall direction of the study at the site level. Many sites will have study coordinator who will be responsible for consenting and enrolling patients, conducting follow-up, inputting data for local subjects, and obtaining medical records for site monitoring purposes. At other sites, the PI or a medical trainee (fellow or resident) may be responsible for study coordinator duties. The clinical and data coordinating center will be at MUSC, and will provide project and data management services as well as statistical support. The collective goal of this research team is to ensure the on-budget, on-time execution of the study with the highest possible ethical, regulatory, and scientific integrity.

4.3 Recruitment

The INTERCPT trial will enroll a maximum of 184 patients over approximately 2½ years. Therefore an approximate enrollment goal of 4 patients per site per year is necessary. We believe that this enrollment requirement is achievable given the volume of MHO patients seen annually at the participating centers.

4.4 Estimated Study Duration

Initiation of Study	3 months
Initiation of Study at All Sites	6 months
Subject Recruitment	28 months
Pre-Treatment/Treatment/Follow-up	6 months
Site Close Out/Analysis and Reports	6 months
Total:	49 months

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

Any patient with cholestasis due to suspected MHO who provides written informed consent AND:

Has **all three** of the following:

(1) Age ≥ 40 (to reduce the likelihood of enrolling patients with obstruction due to primary sclerosing cholangitis)
(2) Cholestatic liver function tests, including serum alkaline phosphatase level ≥ 300 IU/L and bilirubin level ≥ 3.7 mg/dL
(3) Radiographic evidence of a biliary hilar stricture *OR* intrahepatic *but no extrahepatic* biliary ductal dilation

5.2 Exclusion Criteria

(1) Known radiographic evidence of a Bismuth-Corlette type 1 biliary stricture
(2) Known diagnosis of primary sclerosing cholangitis *without* suspicion of dominant hilar stricture
(3) Recent cholecystectomy, liver resection, or biliary surgery within 12 months
(4) Known Mirizzi syndrome
(5) Known IgG4-mediated cholangiopathy
(6) Significant liver metastatic disease interfering with safe/effective PTBD
(7) Significant peri-hepatic ascites interfering with safe/effective PTBD
(8) Known UGI tract obstruction precluding ERC
(9) Known regional malignant-appearing adenopathy or extra-biliary mass, indicating the need for concurrent EUS-FNA
(10) Prior ERCP or PTBD for hilar obstruction
(11) Surgically altered luminal anatomy other than prior Billroth reconstruction
(12) Standard general contraindications to ERCP or PTBD (e.g. hemodynamic instability, uncorrected coagulopathy)
(13) Pregnancy
(14) Inability or unwillingness to follow study protocol

6.0 SUBJECT RECRUITMENT

6.1 Screening of Potential Subjects

All patients presenting to participating study centers with cholestasis and suspicion of MHO will be screened for eligibility by reviewing inclusion and exclusion criteria. Ongoing study recruitment efforts at each center will include the maintenance of a Screen Failure Log for the purpose of documenting the center population from which the subjects in this trial are drawn who are not eligible for the study. All patients who meet inclusion criteria, but are ultimately not randomized will be recorded on the INTERCPT Screen Failure Log. A reason for exclusion for each of these patients will be recorded. Further details on the completion of the Screen Failure Log are located in the Manual of Procedures (MoP).

7.0 SUBJECT Consent

7.1 Pre-Consent Eligibility Assessment

Eligibility assessment will include*:*

1) Pregnancy test (if not recently done) in any woman with anatomical capacity to bear a child who is not at least 12 months post-menopausal.
2) Verification that all inclusion/exclusion criteria have been evaluated correctly;
3) Evaluation and documentation of relevant medical history;
4) Verification that all required information has been documented;

7.2 Presentation of Informed Consent

Consent will be obtained by an investigator or study coordinator after eligibility is confirmed by an investigator. The initial consent will be the most recent IRB-approved version. During the consent process the objectives of the study, as well as the risks and benefits of enrolling will be explained in detail to potential subjects.

Informed consent will generally be obtained from subjects in the clinic or hospital room. The Informed Consent process will be documented in the subject record to include a review of the trial, the informed consent document, and that subject questions were answered prior to signature of the consent. Subjects will receive a copy of the signed and dated informed consent document and the original signed and dated consent form will be placed in the subject record. Original informed consent documents will be maintained on-file at each participating center. Once consented and enrolled into the trial, subjects will be issued a unique code to be used on data collection forms and other research records throughout the duration of the trial. Consent to procure outside medical records will also be obtained from study subjects in the event they are admitted to an outside facility after the ERC or PTBD.

To maximize recruitment, potential study subjects will be provided a balanced and complete explanation of the risks, benefits, merits, and disadvantages of both PTBD and ERC as outlined in the background section of this protocol, emphasizing that the optimal approach in this situation is truly unknown.

7.2.1 Optional Telephone eConsent

In some cases, potentially eligible outpatients may be identified by the research team when they are referred directly for an ERC or PTBD. When this is the case, the investigator or study coordinator may contact the patient via telephone for a formal discussion of the trial and will go through the eConsent document on REDCap. If the patient agrees to participate, the investigator or study coordinator will obtain the patient's electronic consent (eConsent) in REDCap and randomization will occur to determine which procedure will be scheduled.

8.0 STUDY PROCEDURES

8.1 Screening/Baseline Visit

The following events will occur during the baseline screening visit once a member of the study team becomes aware of a potentially eligible study candidate.

8.1.1 Informed Consent

A written informed consent form will be reviewed and signed by each subject before any study-related procedures are performed. Investigators or designated staff may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent.

Optional: An eConsent may be obtained if the patient is identified prior to arriving at the study institution.

8.1.2 Medical History & Record Review

Study-relevant medical history will be reviewed and documented.

8.2 Randomization

Eligible patients who provide informed consent will be randomized in 1:1 fashion to PTBD or ERC as the first intervention using a web-based electronic randomization system that will be accessed from a computer, tablet, or smartphone at the enrolling site. The randomization schedule will be generated centrally at the data coordinating center and will ensure treatment balance within site.

NOTE: SUBJECTS NOT MEETING INCLUSION CRITERIA OR IDENTIFIED AS INELIGIBLE BASED ON EXCLUSION CRITERIA WILL *NOT BE RANDOMIZED*.

- Subjects who meet inclusion criteria but have an exclusion criterion or are not consented for any reason will be recorded in the Screen Failure Log along with the reason for eligibility exclusion or unwillingness to provide consent.
- Consented subjects who are not randomized will be recorded in the Screen Failure Log along with the reason for eligibility exclusion.
- Consented subjects not eligible for randomization will receive continued medical treatment per standard of care at each institution and appropriate details will be documented in the subject research record.

8.3 PTBD & ERC Procedures

The activities surrounding the PTBD and ERC procedures are described in detail below.

8.3.1 Standard Medical Procedure Consent (Non-Research)

Subjects will review and sign a standard medical consent form (non-research) specific to PTBD or ERC after randomization, generally immediately prior to the PTBD or ERC. Typically, the patient will be consented for the study 1-24 hours prior to their clinical procedure. In some cases, research consent may be obtained in the clinic setting several days or weeks prior to the clinical procedure. The preparation is the same for both ERC and PTBD.

8.3.2 Risks/Anticipated Adverse Events Related to PTBD and ERC

For the INTERCPT trial, the following AEs are anticipated based on the known complications of PTBD, ERC, and associated interventions[3,4]. In many subjects, therefore, these events will be considered "expected." On the other hand, in other individual subjects, these events may be adjudicated to be "unexpected" in view of their severity, their timing, and/or the medical context in which they occur. The site PI will review all SAEs for expectedness and take all factors carefully into account in deciding whether he/she believes that the event is expected or unexpected.

Cardiopulmonary (Both PTBD & ERC): The effects of sedation/anesthesia and the stresses of the ERC & PTBD procedure may result (during procedures or in the early recovery period) in pulmonary dysfunction (e.g. hypoxia, pneumonia), or cardiac compromise (e.g. dysrhythmia, myocardial ischemia, infarction). Most of these events can be managed by standard conservative means, but some may result in the procedure being aborted, and/or the need for subsequent hospitalization

Acute pancreatitis (More common after ERC than PTBD): This is defined according to the Atlanta criteria *or* Cotton's consensus criteria for post-ERCP pancreatitis.
Atlanta criteria: Two of the following: 1) abdominal pain consistent with acute pancreatitis; 2) pancreatic enzymes > 3 ULN; 3) characteristic imaging findings.
Cotton's consensus criteria: All three of the following: 1) abdominal pain consistent with acute pancreatitis; 2) pancreatic enzymes ≥ 3x ULN 24 hours after the procedure; 3) hospitalization or prolongation of existing hospitalization by at least 2 nights.

Cholangitis (Both PTBD & ERC): This is defined as a clinically apparent infection originating within the biliary system. Ascending cholangitis typically manifests as fever and other signs of local or systemic infection (such as leukocytosis, tachycardia, hypotension) with associated evidence of biliary obstruction (such as increase in liver function tests, or radiographic of biliary obstruction).

Hemorrhage (Both PTBD & ERC): This is defined as clinical symptoms that could reflect bleeding (such as gastrointestinal blood loss or abdominal pain due to a subcapsular hematoma or intra-abdominal bleed) along with a decrease in hemoglobin of at least 2 g/dL. Bleeding with significant implications occurs in cases that require hospitalization for transfusion or another invasive intervention to achieve hemostasis.

Perforation (ERC only): This is defined as the development of a defect in the gastrointestinal tract wall that is recognized during or after the procedure. In ERC, this can occur during sphincterotomy, when the cut extends through the duodenum wall into the

retroperitoneum (tissues behind the duodenum and pancreas). Less commonly, the endoscope itself can cause a perforation in the wall of the esophagus, stomach or intestine. If recognized, this type of perforation can usually be closed endoscopically, but may require surgical intervention. Most perforations can be treated medically (with IV fluids, antibiotics, and nasogastric suction), but severe cases may require surgery.

Bile leak/biloma (Both PTBD & ERC): This is defined as clinical symptoms that are attributable to leakage of bile into any space outside the biliary system. Bile leaks may be identified during the procedure by extravasation of injected contrast or afterwards through scintigraphy, cross-sectional imaging, or percutaneous fluid sampling. Leakage of bile may be of no clinical consequence. When this phenomenon is associated with clinical symptoms, it will be considered an adverse event.

Pneumothorax (PTBD only): This is defined as air or another gas within the pleural space requiring additional observation or treatment. In the INTERCPT trial, a pneumothorax will be most likely due to an iatrogenic injury to the lung. This may be asymptomatic or result in significant clinical symptoms. When a pneumothorax requires additional observation to ensure absence of progression, or treatment such as 100% oxygen administration or chest tube placement, it will be considered an adverse event.

Pleural effusion (PTBD only): This is defined as fluid in the pleural space that requiring additional diagnostic testing or treatment. In the INTERCPT trial, a pleural effusion could be iatrogenic in nature. This may be asymptomatic or result in significant clinical symptoms. When a pleural effusion requires additional diagnostic testing or treatment such as thoracentesis or chest tube placement, it will be considered an adverse event.

Hospitalization (Both PTBD & ERC): Adverse events after both procedures are generally managed in the inpatient setting. Both procedures may require routine post-procedure hospital observation, although this is more likely to occur after PTBD.

8.3.3 Pre-Procedure Preparation

Pre-procedure preparation will follow usual clinical care.

8.3.4 Participating Proceduralists

All study PTBDs and ERCs will be performed or directly supervised by board certified interventional radiologists or gastroenterologists with specialized expertise in these procedures who are faculty physicians at participating study centers. A proportion of study cases will involve trainees at varying stages of proficiency. The extent of participation of the trainee in the study procedure will be left to the discretion of the attending proceduralist.

8.3.5 Procedure

All components of the PTBD or ERC and related interventions will be dictated by treating physicians per usual care. Specifically, the technical approach to drainage (e.g. bilateral vs. unilateral) and tissue sampling (e.g. brushing, intraductal biopsies, cholangioscopy, fluorescence in situ hybiridization, etc.) will be determined by

treating physicians and proceduralists performing the PTBD or ERC. Hospital admission or prolongation of hospitalization after PTBD or ERC will be dictated by treating physicians. If a tissue diagnosis is needed, study personnel (coordinator or site PI) will discuss the importance of adequate tissue sampling with the proceduralist prior to the index PTBD or ERC. A tissue diagnosis is not mandatory for enrollment in INTERCPT. In some patients – mainly those without a pre-existing tissue diagnosis — diagnostic sampling of the stricture will be necessary for clinical (not research) purposes. Although it is the clinicians' responsibility to recognize that a tissue diagnosis is needed, it is possible that a patient's participation in INTERCPT may lead to the erroneous assumption by the person performing ERC or PTBD that a tissue diagnosis has already been made. To protect against this confusion, when a tissue diagnosis is needed, the coordinator or site PI will discuss the importance of adequate tissue sampling with the proceduralist prior to the index procedure.

8.3.6 Additional Interventions

All decisions pertaining to the need for repeat procedures to address inadequate drainage or incomplete tissue sampling or the decision to refer for the alternate procedure will be dictated by treating physicians. Thus, subsequent interventions, including additional PTBD or ERC, will NOT be dictated by the INTERCPT protocol.

8.4 Follow-Up Assessments

All enrolled subjects will be followed for 6 months after the index procedure primarily through review of their medical records to obtain laboratory clinical, and procedural information from regularly scheduled clinical appointments. If the research personnel are not able to obtain enough information from clinical appointments, a member of the research team will contact the patient at 3 months and 6 months after his/her PTBD or ERC procedure. The purpose of these phone calls would be to ask questions about whether the patient has sought care at other medical facilities and about quality of life.

8.4.1 Post-Intervention Evaluation

During the 6-month period, pertinent follow-up data will be collected in an ongoing fashion by study personnel (gastroenterologist, interventional radiologist, research fellow, clinical trainee, or research coordinator) on a study-specific case report form and subsequently input electronically into the study database.

Subjects' medical records will be reviewed only as long as needed to collect all follow-up data, but not beyond 2 years after enrollment. The purpose of these reviews will be to collect ERC & PTBD results, additional ERC & PTBD findings,

hospitalizations, and laboratory or radiology data from the time of the index procedure until 6 months after. Clinical data will be stored indefinitely as long as consent has not been withdrawn.

8.4.2 Quality of Life Evaluation

When possible, between 2 and 3 months after randomization, a quality of life assessment using one or more validated instruments will be administered to enrolled subjects by study personnel either in person during a routine clinical follow-up visit or by telephone. These assessments may include the SF-12 and the PROMIS Global Health Scale. This will be encouraged in all participants but is not mandatory.

Any suggestion of suicidality on the QOL assessments will trigger immediate notification of the subject's primary physician or mental health clinician if available. Suicide hotline information will also be provided. Subject who answer, "All of the time" on questions 11&12 on the SF-12 or "Poor" on question 4 on the PROMIS Global Health Scale will trigger notification of the subject's primary physician or mental health clinician if available.

9.0 DISCONTINUATION OF PARTICIPATION

9.1 Subject Withdrawal

The subject has the right to voluntarily withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution.

If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subject data will be included in the analysis up to the date of the consent withdrawal.

A distinction should be made between subjects who fail to complete all forms on schedule and those who withdraw consent. Missed or rescheduled visits will be documented, but the subject will continue to be followed in the future according to protocol requirements, and all follow-up data will be included in the protocol-specified analysis.

9.2 Subject Removal from Study

Subjects may be removed from the study if any of the following events occur:

(1) Refusal of the subject to remain in the study (i.e. consent withdrawal).
(2) If the physician believes it is in the subject's best interest to discontinue participation in the study.
(3) Administrative reasons, e.g., termination of the study.

9.3 Procedure for Discontinuation

The procedure to be followed at the time a subject either discontinues participation or is removed from the study is:

(1) Adverse event assessment.
(2) Attempt to perform final follow-up evaluations.
(3) Complete an explanation of why the subject is withdrawing or withdrawn.

9.4 Subject Lost to Follow-Up

Subjects may be contacted by research personnel to determine whether they have received care at another facility. If so, records will be obtained from that facility in order to collect study data. A plan of action for following up on subjects who cannot be contacted via telephone is outlined in the Manual of Procedures. When all possible attempts to locate the subject have failed, that subject will be considered 'lost to research follow up'.

9.5 Re-entering the Study

If a subject who has withdrawn from the study voluntarily expresses interest in returning to complete the study, the subject can be re-entered.

9.6 Subject Transfers

Whenever a subject's medical care transfers to another clinical setting, every attempt must be made to obtain continued follow-up data.

10.0 OUTCOMES DEFINITIONS

10.1 Primary

The primary endpoint is s*uccessful biliary drainage*, defined as a 50% reduction from baseline in bilirubin level within 3 weeks after the study intervention without additional ERC or PTBD during that timeframe. This will be assessed on the basis of existing medical records in which we expect repeat laboratory evaluation to be obtained and documented within 3 weeks after the index procedure. At the conclusion of the study, the proportion of subjects who achieve successful biliary drainage will be compared between treatment arms.

10.2 Secondary

The following are secondary endpoints:

Successful biliary drainage (alternate definition), defined as improvement in the serum bilirubin level to $\leq$2.5 mg/dL as a result of the index (randomization) intervention without the need for additional ERC or PTBD. The patient will be

considered to have met the primary endpoint even if the bilirubin level rises back above 2.5 during the 6-month follow up period. This bilirubin threshold was chosen because it is the threshold most commonly used by oncologists to administer chemotherapy. Since the rate of jaundice resolution is highly variable and dependent on multiple factors, the outcome will not be confined to a pre-specified timeframe.

Adverse events related to PTBD or ERC, defined according to standard consensus guidelines documents published in the interventional radiology[3] and gastroenterology[4] literature respectively. These definitions are provided in the Manual of Procedures and the Safety Monitoring Plan.

Adequate tissue diagnosis, defined as a definitive histologic diagnosis of malignancy documented in the subject's medical record among patients in whom the diagnosis is unknown. We recognize that a fraction of patients will not have malignant hilar obstruction or may not require a tissue diagnosis, and that a gold standard diagnostic test will not be available within the follow-up period in many patients who are not diagnosed with cancer. We do, however, expect that patients with cancer in whom a tissue diagnosis is needed & possible will be allocated evenly between study groups.

Number of ERC, PTBD, and hospitalizations during the follow-up period.

At the conclusion of the study, the proportion of subjects with each secondary endpoint will be compared between treatment arms.

11.0 DATA Collection, Management, and Quality Control Procedures

11.1 Data Management

Data management will be handled by the Statistical and Data Management Center (SDMC) which is housed in the Data Coordination Unit (DCU) in the Department of Public Health Sciences at the Medical University of South Carolina (MUSC). All study activities will be conducted in coordination with the study PI and the clinical sites, and will use an electronic data acquisition method wherein all clinical data on randomized subjects will be entered directly by the site personnel. The latest version of each CRF will be available as a PDF file on the study website for use as worksheets and source documents by study personnel.

The study data will be managed (including data queries) using the WebDCU™ system. This user-friendly web-based clinical trials management system, developed by the DCU, will be used for subject randomization, data entry, data validation, project progress monitoring, subject tracking, and secure data transfer.

11.2 Site Monitoring

Study data will be monitored by the project managers on a routine basis for completeness, timeliness, logic, and consistency. Data accuracy will be verified centrally on a quarterly basis by the project managers and principal investigator through review of randomly selected (redacted) medical records. Overall, we intend to centrally review medical records for ~15% of all study participants. Discovered discrepancies between site-provided data and medical records will be addressed through discussions between the project manager and study site personnel. Site-specific accrual will be monitored centrally on a continual basis. To protect against significant selection bias by site, data from sites that enroll <4 subjects/year will be censored during a subgroup analysis intended to evaluate selection bias. Ideally the intended sample size of 184 would be comprised of uncensored subject data, suggesting that the overall sample size might be larger.

11.3 Data Security and Confidentiality

During the course of the trial, user access to the data housed within the study database, treatment assignment, and files with study outcomes will be restricted to core study staff at MUSC.

In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent. No information, which identifies a specific person, hospital, or physician, will be released to, or discussed with anyone other than study staff members.

Because the SDMC uses a web-based system, source documents and CRFs will remain at the participating sites. The study database only identifies study subjects by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password protected system. All collected information about a subject will be stored by a unique identification code. All MUSC study personnel are certified by the NIH Office of Human Subjects Research in the Protection of Human Research Subjects course.

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size Calculation

Given patient preferences to avoid extracorporeal tubes as well as the other perceived advantages of ERC, PTBD would have to be at least 20% more effective in achieving successful biliary drainage to change clinical practice. Assuming that PTBD will be 90% effective in achieving successful biliary decompression, we estimate that 160 patients (80 per study group) would provide a power of at least 85% to detect a 20% absolute difference between study groups on the basis of Fisher's exact test, with a two-sided significance level of 0.05. To address potential

losses to follow-up, the sample size is inflated by 15%. Thus a total of 184 subjects will be randomized.

12.2 Statistical Analyses

For analysis of the primary endpoint, we will use a chi-squared or Fisher's exact test to compare the proportion of patients achieving successful biliary drainage in the PTBD and ERC groups using the intention-to-treat (ITT) principle. All randomized subjects will comprise the ITT population. The primary analysis will not adjust for potential variability by study site on the primary outcome measure in order to report generalizable results from the trial. As a secondary analysis of the primary outcome, we will examine center differences by including study site as a covariate in the analysis model to examine any center impact on the estimated treatment effect. Since there will be roughly 25 centers, study site will be modeled as a random effect. Predictors of response in the PTBD group, the ERC group, and the entire cohort will be explored using a multivariable logistic regression model with successful biliary drainage as the dependent variable. For analysis of secondary endpoints, dichotomous variables will be compared using a Fisher's exact or chi-squared test and continuous variables will be compared using a two-sample comparison of means. For all pre-specified analyses, a final two-sided $p < 0.05$ will indicate statistical significance. There will be no adjustment for multiple comparisons in the pre-specified secondary analyses, but all additional exploratory analysis results will be interpreted more conservatively using a significance level of 0.01.

Recognizing that the study population may be heterogeneous in ways which could differentially impact the success of ERC vs. PTC, we plan on performing pre-defined exploratory analyses of treatment differences in the primary outcome, adjusting for possible prognostic variables including: 1) age, 2) BMI, 3) Charlson comorbidity index, 4) presence of proven malignancy, 5) stricture Bismuth type, 6) presence of significant unilateral lobar atrophy, and 7) recruitment at a center enrolling an average of ≥ 4 patients/year. Each covariate will be evaluated individually first in a logistic regression model that includes an interaction effect with the treatment. Interactions will be examined at significance level of 0.15, though the trial may be underpowered to assess interactions. If significant (statistical and clinical) interaction is concluded, subgroup analyses may be considered. A multivariable model that includes covariates that contributed significantly as treatment modifiers individually may then be constructed.

12.3 Interim Analysis

There will be no planned interim analyses.

12.4 Data and safety monitoring plan (DSMP)

Study data and safety will be monitored by a PI-appointed Data and Safety Monitoring Board (DSMB). This committee will be composed of 3 persons independent of the trial investigators. The overall goals of the committee will include the following: 1) identify unacceptably slow rates of accrual, 2) identify high rates of ineligibility determined after randomization, 3) identify protocol violations that suggest clarification of changes to protocol are needed, 4) identify unexpectedly high dropout rates that threaten the trial's ability to produce credible results, 5) ensure the credibility of the study, 6) ensure the validity of study results, and most importantly, 7) protect the safety of trial participants. The safety review committee will meet twice annually, or more frequently if deemed necessary. If irregularities are identified in any of the goal areas listed above, the committee will propose changes to the protocol or study infrastructure in order to remedy the problem. In the event of a severe problem, the committee may advise termination of the study.

13.0 REGULATORY AND ETHICAL OBLIGATIONS

13.1 Informed Consent

In accordance with federal regulations (45 CFR 46) and guidelines (Federal Register, May 9, 1997, Vol. 62, Number 90–ICH Good Clinical Practice Consolidated Guideline), it is the investigator's responsibility to ensure that legally effective informed consent is obtained from the participant before participating in an investigational study, after an adequate explanation of the purpose, methods, risks, potential benefits and participant responsibilities of the study. Procedures that are to be performed as part of the practice of medicine and which would be performed whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent.

Each subject must be given a copy of the signed and dated informed consent. The original signed consent must be retained in the institution's records and is subject to review by the sponsor, coordinating center, federal representative or representative from another agency that performs the same function, and the IRB responsible for the conduct of the institution. ICH Good Clinical Practice guidelines will be followed to the extent required by the federal regulations.

Informed consent will be obtained by either the principal investigator or by individuals approved by the clinical center's principal investigator. Informed consent will be obtained from the subject or subject's legally acceptable representative after the details of the protocol have been reviewed. The individual responsible for obtaining consent will assure, prior to signing of the informed consent, that the subject has had all questions regarding therapy and the protocol answered.

13.2 Institutional Review Board

In accordance with federal regulations (45 CFR 46) and guidelines (Federal Register, May 9, 1997 Vol. 62 Number 90 - ICH Good Clinical Practice Consolidated Guideline), all research involving human subjects and changes to the research plan must be reviewed and approved by a local IRB.

13.2.1 Initial Review and Approval

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the Clinical Center's IRB for written approval.

13.2.2 Amendments

The Principal Investigator must agree to, and obtain approval from the IRB for, all protocol amendments and revisions to the informed consent document as dictated by Executive Committee. The Principal Investigator at each clinical center must obtain approval from the IRB for all revisions to the informed consent document.

13.2.3 Annual Renewal

The Principal Investigator will be responsible for obtaining annual IRB approval renewal throughout the duration of the study.

13.3 Pre-Study Documentation Requirements

The Principal Investigator at each Clinical Center is responsible for providing all required regulatory documents to the INTERCPT Project Managers PRIOR to recruitment (located in the current version of the Manual of Procedures on WebDCU™).

13.4 Subject Confidentiality

The Principal Investigator at each Clinical Center must ensure that subject confidentiality is maintained. Enrolled subjects will be identified on any study documentation only by their initials and a study identification number generated by WebDCU™.

14.0 ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Study Termination

The study will be complete when all subjects have had their final study assessments. The Principal Investigator reserves the right to terminate the study if new

information becomes available on the safety or efficacy of the study intervention or if such action is justified.

The Clinical Center reserves the right to terminate the study according to the contract. The investigator is responsible for notifying the IRB in writing of the trial's completion or early termination.

15.0 Organizational infrastructure

15.1 Executive Committee

The Executive Committee (EC) is composed of the study PI, the SDMC PI, and the Project Managers.

The EC prepared the final protocol and will provide long-term scientific direction for the study at the operational level. The EC will advise and assist the study team on operational matters, monitor the performance of the clinical centers and communicate requests for any proposed ancillary changes in the protocol to the DSMB. The Executive Committee will review performance of each participating institution to identify and implement solutions to problems that arise. In addition, the collection, review and oversight of dissemination of SAE occurrences and other important events pertinent to the study will be the responsibility of the Executive Committee; as well as communication among all components of the study participants.

Throughout the study, the Executive Committee will meet monthly and *ad hoc* as needed. Additional details including membership information are located in the current version of the Manual of Procedures.

15.2 Standing Committees

Potential standing committees will be convened to address key study issues, such as ancillary studies and publications.

15.3 Statistical and Data Management Center

The Statistical and Data Management Center (SDMC) is housed in the Department of Public Health Sciences Data Coordination Unit (DCU) at MUSC. Lydia Foster will assume overall responsibility of the SDMC. The SDMC will provide data management and analysis for the Trial. Specifically, they will: (1) develop the case report forms; (2) create and maintain the study database, including subject registration/randomization; (3) develop and maintain a Data Management Plan; (4) assure data security and appropriate archiving of data files; (5) provide statistical support for the trial for the DSMB reports and final anlayses; and (6) transfer the final datasets to the PI at the end of the trial. The MUSC DCU, which will house the SDMC, has extensive experience with all aspects of data management for multicenter clinical trials, and is in full compliance with the Good Clinical Practice (GCP) guidelines and regulations for conducting clinical trials. All systems used

in the management and storage of clinical trial data are maintained on site at the offices of DCU.

16.0 REFERENCES

1. Paik WH, Park YS, Hwang JH, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest Endosc 2009;69:55-62.

2. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, et al. Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma. J Gastroenterol Hepatol. 2013;28:593-607.

3. Saad WE, Wallace MJ, Wojak JC, et al. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. J Vasc Interv Radiol 2010;21:789-95.

4. Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017;85:32-47.

Appendix B: Possible factors that contributed to prohibitively slow enrollment

1. Unexpectedly large number of MHO patients referred to study centers after the initial drainage procedure was already performed.

2. Outpatient referrals for MHO that are not seen in clinic could not be enrolled because there was no mechanism to approach/consent patients via telephone, which would have allowed them to present to the study center for their randomization procedure. Asking patients to present for ERCP and then potentially randomizing them to PTC on a subsequent day was considered inappropriate.

3. Patient and referring gastroenterologist bias in favor of ERCP, leading to declined consent. Conversely, at least 2 patients elected to decline consent and undergo PTC after learning that observational data suggest this procedure to be a faster pathway toward a normal bilirubin level.

4. Institutional/clinician bias in favor of ERCP or PTC. Even though each site principal investigator (PI) expressed equipoise in randomizing patients to ERCP or PTC, other key clinicians, such as interventional radiologists, surgeons, oncologists, and other gastroenterologists may have favored one approach over the other.

5. Even if bias in favor of one procedure was not a factor, study personnel may not have been informed of potentially eligible subjects by clinicians because of the disruptive nature of randomization, which represents a path of higher resistance and interferes with patient/clinical flow.

6. Insufficient time for busy clinician-investigators to devote to identifying potentially eligible patients and approaching them before the drainage procedure has been selected. This may have been exacerbated by the lack of grant support.