THOMAS JEFFERSON UNIVERSITY
Kimmel Cancer Center

PREOPERATIVE ENDOSCOPIC BILIARY DRAINAGE WITH SELF EXPANDING METAL STENTS (SEMS) VS. DIRECT SURGICAL RESECTION FOR PATIENTS WITH SEVERE OBSTRUCTIVE JAUNDICE

Principal Investigator:	Thomas Kowalski, MD Gastroenterology and Hepatology 132 S. 10th Street Suite 585 Philadelphia, PA 19107 (215) 955-8900 Harish Lavu, MD Hepatopancreaticobiliary Surgery 1100 Walnut Street 5th Floor Philadelphia, PA 19107 (215) 955-9402
Co-Investigator(s):	David Loren, MD Ali Siddiqui, MD Haroon Shahid, MD Benjamin Leiby, PhD Gastroenterology and Hepatology 132 S. 10th Street Suite 585 Philadelphia, PA 19107
Funding Sponsor:	This is a non-funded study
Regulatory Sponsor:	
IND Number:	
Study Product:	
Protocol Number:	16D.759

CONFIDENTIAL

Table of Contents

List of Abbreviations

SEMS; Self Expanding Metal Stents

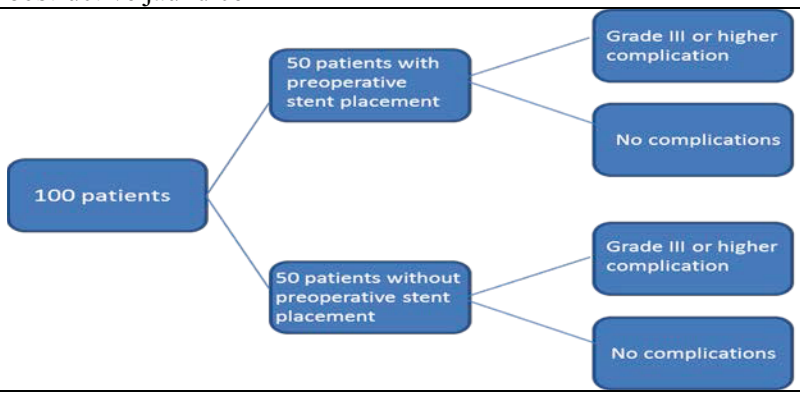
ERCP; Endoscopic Retrograde Cholangiopancreatogram

CBC; Complete Blood Count

CMP; Comprehensive Metabolic Panel

INR; International Normalized Ratio

1 Study Summary

Title	Preoperative Endoscopic Biliary Drainage with Self Expanding Metal Stents (SEMS) vs. Direct Surgical Resection for Patients with Severe Obstructive Jaundice
Short Title	Pre-surgery biliary stent placement vs. direct surgery in patient with obstructive jaundice
Protocol Number	
Phase	N/A
Methodology/Study Design	Randomized control trial
Study Duration	24 months
Study Center(s)	Thomas Jefferson University
Objectives	Investigate the advantage of using biliary SEMS in patients with severe jaundice prior to surgical resection
Number of Subjects	100
Diagnosis and Main Inclusion Criteria	Patients with periampullary cancer with profound jaundice
Study Therapy, Dose, Route, Regimen	Pre-operative SEMS placement vs direct surgical resection
Duration of administration and follow-up	Patient outcome data will be monitored at 30 days and 90 days post resection surgery.
Reference therapy	Direct surgery without stent placement
Statistical Methodology	This is a superiority trial of early surgery without biliary stenting, as compared with preoperative biliary drainage in patients with severe obstructive jaundice
Schema	

2

1.0 INTRODUCTION

Pancreatic cancer is the second most common digestive cancer and fourth leading cause of cancer death in the United States for both men and women. Pancreatic tumors arising in the peri-ampullary region present with biliary obstruction in 64-77% of cases. Preoperative biliary decompression has been advocated in an attempt to reduce postoperative complications following attempted curative-intent surgery.

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Specific Aims and Hypothesis

The primary aim of this study is to compare the 30 and 90-day overall/cumulative grade III or higher complication rates between patients with severe obstructive jaundice undergoing preoperative endoscopic biliary drainage with SEMS and patients undergoing direct surgical resection. In this study, One arm undergoes preoperative biliary drainage followed by surgery and the other arm undergoes surgical resection without prior biliary drainage . Secondary aims will be to compare surgical outcomes including mortality, intra-operative parameters, hospital length of stay, ICU length of stay, readmission rate and time to commencement of adjuvant treatment.

1.2 Background and Rationale

Despite the fact that endoscopic and percutaneous placement of biliary stents is technically successful in 90-95% of cases, routine preoperative biliary drainage for pancreatic cancer remains controversial.[4, 5] Pooled data from retrospective studies published over the past several years have shown similar rates of 30-day mortality after pancreaticoduodenectomy in those who have undergone biliary decompression as compared to those who have not. A few studies have suggested that routine preoperative drainage in patients undergoing surgery for cancer of the pancreatic head may increase overall complications, likely due to complication related to the endoscopy itself (i.e. pancreatitis, bleeding, perforation) and complications related to stent failure.[6] In the largest, multicenter, randomized trial to date, patients were randomly assigned to undergo either endoscopic preoperative biliary drainage for 4 to 6 weeks, followed by surgery, or surgery alone after diagnosis. In this study, endoscopic preoperative biliary drainage did not have a beneficial effect on the surgical outcome but rather was associated with an increase in serious complications.[7]

On the other hand, outcome measures have not been standardized and the lack of complete data on surgical complications following preoperative drainage make direct comparisons difficult and potentially biased. Many of the prior studies used plastic stents for preoperative decompression, which when compared to self-expanding metal stents (SEMS) result in greater rates of re-intervention and cholangitis. A recent meta-analysis of 1989 patients showed that SEMS have higher stent insertion success, lower risk of stent occlusion, lower re-intervention rate, fewer therapeutic failures, and fewer episodes of cholangitis compared to plastic stents making them the optimal choice for biliary decompression.[8] Also a recent randomized controlled trial confirmed that SEMS are superior to plastic stents with regard to functional stent time and showed that the total health care cost is similar for placing SEMS or plastic stents even in patients with survival less than 3 months.[9] Thus, this study will provide unique perspective on the potential advantages of biliary decompression using SEMS. Additionally, prior studies have excluded severely jaundiced patients (serum bilirubin > 14.6), a population that may have derived the

greatest benefit from preoperative drainage, since these patients are more likely to have impaired liver function. In fact, patients with malignant obstruction who present with severe jaundice (>10mg/dL) are likely at higher risk for poor outcome following surgery.[10] These patients may also benefit from preoperative drainage to alleviate pruritus and correct coagulation disturbances.[11] Thus, although preoperative biliary drainage may not be routinely recommended for all patients with malignant biliary obstruction, drainage may be potentially advantageous for those patients with severe jaundice using a SEMS.

1.3 Study Therapy

Both preoperative SEMS placement and direct surgical resection are considered acceptable standard of care in this patient population.

SEMS (Wallflex, Boston Scientific) will be used. The WallFlex Biliary Stent System is FDA-cleared in the US, and is indicated for use in the palliative treatment of biliary strictures produced by malignant neoplasms. Also, the WallFlex Biliary RX Stent is 510(k) cleared for the treatment of biliary strictures produced by malignant neoplasms and relief of malignant biliary obstruction prior to surgery. This represents the first biliary metal stent with labeling to support pre-operative drainage in the US.

1.4 Preclinical Data

Please see clinical data below

1.5 Clinical Data to Date

A recent meta-analysis of 1989 patients showed that SEMS have higher stent insertion success, lower risk of stent occlusion, lower re-intervention rate, fewer therapeutic failures, and fewer episodes of cholangitis compared to plastic stents making them the optimal choice for biliary decompression.[8] Also a recent randomized controlled trial confirmed that SEMS are superior to plastic stents with regard to functional stent time and showed that the total health care cost is similar for placing SEMS or plastic stents even in patients with survival less than 3 months

1.6 Dose Rationale and Risk/Benefits

The study doesn't involve drug administration.

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

The primary aim of this study is to compare the 30 and 90-day overall complication rates between patients with severe obstructive jaundice undergoing preoperative endoscopic biliary drainage with SEMS and patients undergoing direct surgical resection.

2.2 Secondary Objective:

Secondary aims will be to compare surgical outcomes including hospital length of stay, ICU length of stay, readmission rate, disposition from hospital, emergency room visits, urgent care center visits and time to commencement of adjuvant treatment.

3.0 STUDY DESIGN

3.1 General Design

This is a Randomized controlled trial.

ERCP will be performed on those who are randomized to the intervention group with 24 hours of randomization. The patient will be followed at 30 days and 90 days post-operatively.

3.2 Primary Study Endpoints

30 and 90 day- complication rates between patients with severe obstructive jaundice undergoing preoperative endoscopic biliary drainage with SEMS and patients undergoing direct surgical resection

3.3 Secondary Study Endpoints

Secondary aims include the total number of complications, intraoperative estimated blood loss, number of required fluid boluses, postoperative hospital LOS, readmission rate, disposition from hospital, time to commencement of adjuvant treatment, emergency room visits, urgent care center visits, and perioperative mortality. Complications will include pancreatic fistula, delayed gastric emptying, intra-abdominal abscess, cardiac complications, respiratory complications, deep vein thrombosis, pulmonary embolism, urinary tract infection, wound infection, acute renal failure, hemorrhage, hepaticojejunostomy leak, and duodenojejunostomy leak. Pancreatic fistula was defined and graded according to the International Study Group of Pancreatic Fistula criteria. Delayed gastric emptying was defined and graded according to the International Study Group of Pancreatic Surgery. Wound infections and urinary tract infection were defined according to the Centers for Disease Control and Prevention guidelines. Cardiac complications were defined according to the American College of Cardiology and renal complications were defined by the Acute Dialysis Quality Initiative.

3.4 Primary Safety Endpoints

Both SEMS placement and direct surgical resection are considered acceptable standard of care practices.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

-Adult patients age >18 regardless of gender or ethnicity
-Patients with peri-ampullary pancreatic cancer.
-Patients with serum bilirubin greater than 10mg/dL
-Adequate birth control

4.2 Exclusion Criteria

-Patients with evidence of distant metastasis on CT or MRI
-Patients anticipated to require vascular reconstruction
-Patients with cholangitis
-Patients who previously underwent biliary decompression for cholangitis by ERCP or PTC
-Patients with low performance score (Karnofsky performance status scale < 50)
-Patients with known preexisting liver disease with associated elevated bilirubin
-Patients who are pregnant or actively breast feeding.

4.3 Gender/Minority/Pediatric Inclusion for Research

Any patient can be included if older than 18 years of age irrespective of gender, color, or ethnicity.

4.4 Subject Recruitment and Screening

One Hundred patients older than 18 years with periampullary cancer presenting with jaundice and total bilirubin greater than 10mg/dL will be included in the study.
Patients will be recruited from clinic (gastroenterology and pancreaticobiliary surgery) or when admitted to the hospital for workup and/or management and will be consented at that time.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

Patients can withdraw from the study at any time. Stent placement is the standard of care and thus subjects who elect to withdraw from the study will continue to have the biliary stent in place and be followed regularly similar to patients that are enrolled in the study.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who elect to withdraw from the study will continue to be followed on a regular basis. Data that is important to the integrity of the final study analysis and the safety profile of the SEMS will be collected after obtaining approval of the subjects.

5.0 STUDY DRUG/THERAPY

5.1 Description

The stents to be used in this study are FDA approved WallFlex Biliary RX Stents (Boston Scientific Corporation, Natick, MA, USA) which are available in diameters of 8 or 10 mm and lengths of 40, 60, and 80 mm.

5.2 Treatment Regimen

Stent to be placed pre-operatively in the intervention group to be removed during surgery.

5.3 Risks

- Pain
- Bleeding
- Fever
- Nausea
- Vomiting
- Bile duct ulceration
- Perforation of the gall bladder due to the stent covering the cystic duct
- Infection
- Inflammation
- Recurrent obstructive jaundice 26% (likely)
- Stent occlusion
- Tumor ingrowth through the stent
- Perforation of duodenum or bile duct
- Stent misplacement
- Tumor overgrowth around ends of stent
- Mucosal hyperplasia
- Cholangitis
- Cholecystitis 10% (likely)
- Pancreatitis 6% (possible)
- Stent migration 8% (possible)

Once again, placement of SEMS is the standard of care for patient with profound jaundice despite the lack of evidence to support this practice.

5.4 Method for Assigning Subjects to Treatment Groups

A randomization schedule will be created by the study statistician using the method of random permuted blocks. Randomization assignments will be loaded into a REDCap database before study enrollment begins. Randomization assignments will be accessed through the REDCap randomization facility.

5.5 Preparation and Administration of Study Drug/Therapy

The intervention group will receive a WallFlex Biliary RX Stents (Boston Scientific Corporation, Natick, MA, USA)

5.6 Subject Compliance Monitoring

The stent will placed by ERCP and won't be removed before surgery unless indicated. Follow up phone calls to ascertain secondary endpoints will be made at 30 and 90 days.

5.7 Prior and Concomitant Therapy

Subject in the study are to continue any medications that they are on. Those who are randomized to the intervention group may be asked to hold antiplatelet/anticoagulation agents prior to the ERCP in coordination with their prescribing doctor.

5.8 Blinding of Study Drug

Unblinded study

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule

Screening:

Patients will be screened in clinic or if admitted as inpatients. Patient must satisfy the inclusion criteria listed above. Patient must carry a diagnosis of per-ampullary cancer. Basic labs will be withdrawn including CBC, CMP and INR.

Randomization

Peri-operative: The patient will be admitted and labs will obtained including CBC, CMP and INR prior to surgery.

Post-operative:

Visit 1: This will be scheduled 3-4 weeks after hospital discharge. Labs and imaging may be ordered by the surgeon if needed.

Follow-up

Patients will be followed up to 90 days after the surgery. A phone call will be placed to the patient by research staff to ascertain secondary endpoints. Jefferson EMR will be accessed to ascertain primary endpoint data.

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

Based on previous data, we assumed an overall grade III or higher complication rate of 50% in the control group. Although we are unsure of the expected rate in the pre-operative biliary stenting group, a 30% or greater reduction in the grade III or higher complication

would be meaningful. The sample size will be 100 subjects (50 per arm). We calculated power under various alternatives for the biliary stenting group complication rate using a two-group large-sample normal approximation test of proportions, with a one-sided significance level of 0.05, to test the null hypothesis that the grade III or higher complication rate in surgery with biliary stenting is greater than or equal to the control rate (50%). We have 84% power to detect a reduction if the true rate with biliary stenting is 25%, 66% power if the true rate is 30%, and 44% power if the true rate is 35%.

7.2 Statistical Methods

Baseline characteristics will be summarized by randomization arm using means, standard deviations, and ranges for continuous variables and counts and frequencies for categorical variables.

Rates of grade III or higher complication rates will be estimated separately at 30 and 90 days. The risk difference will be calculated (stent minus control) with a one-sided 95% confidence interval. If the upper bound of the confidence interval is less than 0 at both times, surgery with biliary stenting will be considered effective at reducing the rate of grade III or higher complications.

Group comparisons with respect to continuous outcomes will be performed using two-sample t-tests or Wilcoxon rank sum tests. Comparisons for categorical outcomes will be performed using chi-square tests or Fisher's exact test. Comparisons for count outcomes will use Poisson regression. Kaplan-Meier analysis will be used to estimate the distribution of time-to-event outcomes. Groups will be compared using the log rank test.

7.3 Subject Population(s) for Analysis

All randomized patients will be included in the analysis as randomized. A per-protocol analysis will be performed if there are any patients who do not receive the assigned surgical technique.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious.

A ***serious adverse event*** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up starts at randomization and ends at 90 days after the surgery.

Preexisting Condition

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

General Physical Examination Findings

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

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

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

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

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded according to the following:

Adverse event	**Start date**	**SAE*** 1.Yes (also complete SAE form) 2. No	**Causality** 1. Unrelated 2. Possibly Related	**Severity** 1. Mild 2. Moderate 3. Severe	**Expectedness** 1. Expected 2. Unexpected	**DATE of assessment and INITIALS of delegated clinician**	**Outcome** 1. Resolved 2. Ongoing	**Date Resolved**	**AE Recorded by (initials)**

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4 Stopping Rules

We will do an interim analysis after reaching 50 patients, and if there is a significant difference (> 20%) in post operative mortality or morbidity in one group versus the other, then the study will be discontinued.

8.5 Data and Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting

A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician/pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs/SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at the participating sites and at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. ***Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days***

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.
- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as

  recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.
- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations/requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made.

  The Thomas Jefferson University Data and Safety Monitoring Committee reviews all AE/SAE's on open protocols. Therefore, once AE/SAE reports from participating site are received by the Thomas Jefferson University Coordinating Site, a copy will be submitted to the TJU IRB/Medical Monitor/DSMB. Medical Monitor and DSMB review and monitoring of participating site AEs/SAEs will follow the TJU DSMP.

9.0 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

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

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

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

9.2 Source Documents

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

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Please refer to CRF in the Appendix

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.0 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related

documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data

collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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

10.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

Coordinating Site Study Team

Representatives from the Thomas Jefferson University Study Team will monitor on site at the participating site (or virtually if geographically impossible) within 4 weeks of the first subject enrolling.

Additional study monitoring by an independent auditing agency will be conducted at 10% and 50% site accrual per the TJU Data and Safety Monitoring Plan. This will either occur on-site, if feasible, or will require participating sites to send TJU all source documents, patient charts, etc. to TJU for the audit.

Study Team Conference Calls

Teleconferences with the PIs, research nurses/coordinators, and regulatory staff will occur quarterly. This will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. Minutes of these discussions will be taken to document the date of these meetings, the participants and the issues that were discussed. Copies of these minutes will be maintained in the Regulatory Binders at both sites.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

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

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES

12.1 Funding Source

This is an unfunded study. The protocol prospectively tracks standard clinical care. It will be supported by the investigators, fellows, residents, and research coordinators in the Department of Surgery and the Division of Gastroenterology. There are no additional costs to the study

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

13.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14.0 REFERENCES

1. **Jemal, A., et al., *Cancer statistics, 2010.* CA Cancer J Clin, 2010. 60(5): p. 277-300.**
2. **Hatzaras, I., et al., *Predictors of survival in periampullary cancers following pancreaticoduodenectomy.* Ann Surg Oncol, 2010. 17(4): p. 991-7.**

3. **Uchida, H., et al., *Ampullary cancer and preoperative jaundice: possible indication of the minimal surgery.* Hepatogastroenterology, 2009. 56(93): p. 1194-8.**
4. ***NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy.* NIH Consens State Sci Statements, 2002. 19(1): p. 1-26.**
5. **Chen, V.K., M.R. Arguedas, and T.H. Baron, *Expandable metal biliary stents before pancreaticoduodenectomy for pancreatic cancer: a Monte-Carlo decision analysis.* Clin Gastroenterol Hepatol, 2005. 3(12): p. 1229-37.**
6. **Bonin, E.A. and T.H. Baron, *Preoperative biliary stents in pancreatic cancer.* J Hepatobiliary Pancreat Sci, 2011. 18(5): p. 621-9.**
7. **van der Gaag, N.A., et al., *Preoperative biliary drainage for cancer of the head of the pancreas.* N Engl J Med, 2010. 362(2): p. 129-37.**
8. **Sawas, T., et al., *Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis.* Gastrointest Endosc, 2015. 82(2): p. 256-267 e7.**
9. **Walter, D., et al., *Cost Efficacy of Metal Stents for Palliation of Extrahepatic Bile Duct Obstruction in a Randomized Controlled Trial.* Gastroenterology, 2015. 149(1): p. 130-8.**
10. **Su, Z., et al., *Factors influencing infectious complications after pancreatoduodenectomy.* J Hepatobiliary Pancreat Sci, 2010. 17(2): p. 174-9.**
11. **Kloek, J.J., et al., *Effect of preoperative biliary drainage on coagulation and fibrinolysis in severe obstructive cholestasis.* J Clin Gastroenterol, 2010. 44(9): p. 646-52.**
12. **Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. 240(2): p. 205-13.**

15.0 APPENDICES

Include any attachments for this study (e.g. study schedule/visit chart from procedures section, Pill Diaries to be used, recruitment materials if applicable, AE Logs from section 5.2, Eligibility Checklist, Drug Reconciliation Form, etc.)

Appendix XX:

Adverse event	**Start date**	**SAE*** 1.Yes (also complete SAE form) 2. No	**Causality** 1. Unrelated 2. Possibly Related	**Severity** 1. Mild 2. Moderate 3. Severe	**Expectedness** 1. Expected 2. Unexpected	**DATE of assessment and INITIALS of delegated clinician**	**Outcome** 1. Resolved 2. Ongoing	**Date Resolved**	**AE Recorded by (initials)**