A Phase III Multicenter, Open Label Randomized Controlled Trial of Cefoxitin versus Piperacillin-Tazobactam as Surgical Antibiotic Prophylaxis in Patients Undergoing Pancreatoduodenectomy

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	Consent Only
Commack	Consent Only
Westchester	Consent Only

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

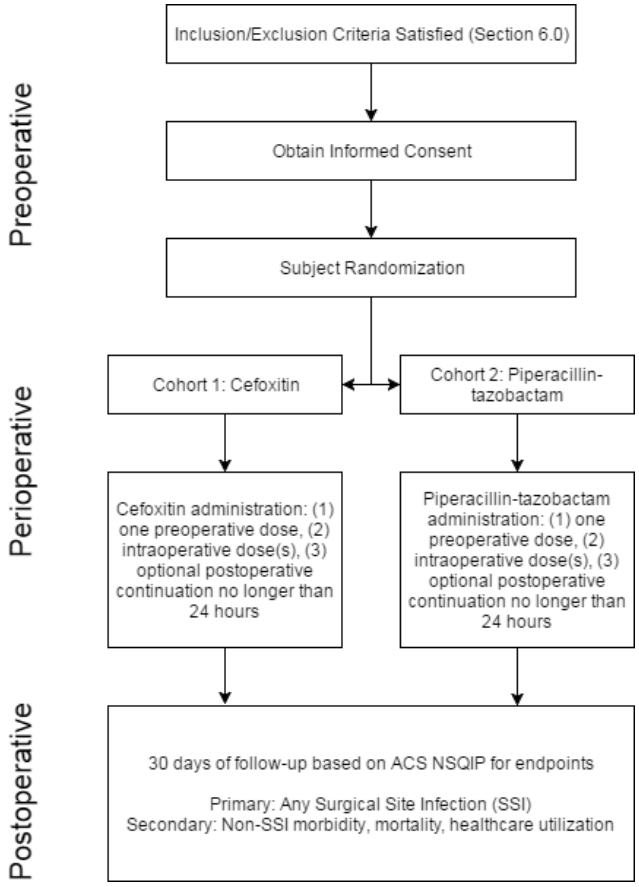
This phase III multi-center, open-label randomized controlled study will determine the most appropriate surgical antibiotic prophylaxis for patients undergoing pancreatoduodenectomy (PD) for all indications. This trial will compare two cohorts of enrolled patients undergoing PD at institutions participating in the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) Hepato-Pancreato-Biliary (HPB) Collaborative. The conduct of this trial will utilize ongoing ACS NSQIP data collection processes. Cohort 1 will be comprised of patients who receive cefoxitin, a second generation cephalosporin, as surgical antibiotic prophylaxis. Cohort 2 will be comprised of patients who receive piperacillan-tazobactam, a broad-spectrum penicillin, as surgical antibiotic prophylaxis. Both cohorts with successful procedures will be followed for 30 days after the index operation according to ACS NSQIP standard operating procedures, with the primary intent to observe differences in postoperative surgical site infection (SSI) rates between cohorts.

Title	A Randomized Controlled Trial of Cefoxitin vs. Piperacillin-Tazobactam as Surgical Antibiotic Prophylaxis in Patients Undergoing Pancreatoduodenectomy
Protocol Number	17-418
Phase	III
Methodology	Open label
Study Duration	24 months
Study Center(s)	Multi-center

Objectives	Primary objective: • To determine if administration of piperacillin-tazobactam as surgical antibiotic prophylaxis results in decreased rates of 30-day surgical site infection (SSI) as compared to the administration of cefoxitin in patients undergoing pancreatoduodenectomy (PD) for all indications. Secondary objective(s): • To determine rates of non-SSI morbidity within 30 days of the operation associated with use of piperacillin-tazobactam as surgical antibiotic prophylaxis as compared to cefoxitin including pneumonia, intraoperative or postoperative unplanned intubation, intraoperative or postoperative pulmonary embolism, ventilator dependence over 48 hours, progressive renal insufficiency or acute renal failure requiring dialysis, urinary tract infection, intraoperative or postoperative stroke or cerebral vascular accident, intraoperative or postoperative cardiac arrest requiring CPR, intraoperative or postoperative myocardial infarction, intraoperative or postoperative transfusion of red blood cells, vein thrombosis requiring therapy, postoperative clostridium difficile colitis, sepsis, sepsis shock, pancreatic fistula, delayed gastric emptying, intraoperative drain management, need for percutaneous drain placement, withdrawal of care, and death during operation or postoperative death within 30 days of procedure. To determine rates of healthcare utilization within 30 days of the operation associated with use of piperacillin-tazobactam as surgical antibiotic prophylaxis as compared to cefoxitin including hospital stay > 30 days, hospital readmission, and unplanned reoperation. Correlative objectives: • To determine the bacterial isolates and their sensitivities from those with postoperative surgical site infections. • To determine the bacterial isolates and their sensitivities from intraoperative bile cultures obtained during PD.
Number of Subjects	Cohort 1: 445 patients Cohort 2: 445 patients Total: 890 patients
Diagnosis and Main Inclusion Criteria	1. Patients undergoing elective pancreatoduodenectomy for either benign or malignant indications. 2. Age ≥18 years of age

Study Product(s), Dose, Route, Regimen	Cohort 1: cefoxitin 2 grams (gm) intravenous (IV) once within 60 minutes prior to PD incision. Cefoxitin should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses. For cases >12 hours, cefoxitin should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 6 hours until end of surgery. It will be discontinued within 24 hours after anesthesia end time. Cohort 2: piperacillin-tazobactam 3.375-4.5 gm IV once 60 minutes prior to PD incision. <u>For centers that employ 3.375 gm doses of IV piperacillin-tazobactam</u>: Piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses. For cases > 12 hours, piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 6 hours until end of surgery. It will be discontinued within 24 hours after anesthesia end time. <u>For centers that employ 4.5 gm doses of IV piperacillin-tazobactam</u>: Piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses. For cases > 12 hours, piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 8 hours until end of surgery. It will be discontinued within 24 hours after anesthesia end time.
Duration of administration	Cohort 1: No longer than 24 hours after anesthesia end time. Cohort 2: No longer than 24 hours after anesthesia end time.
Statistical Methodology	Patients undergoing elective PD will be randomized to receive either cefoxitin or piperacillin-tazobactam, and then will be followed for SSI occurrence for 30 days after the operation according to standard ACS NSQIP data collection processes. A two-sided type I error rate of 0.05 and a power of 0.8 will be used to detect a reduction in SSI rates from 0.2 in the cefoxitin group to 0.13 in the piperacillin-tazobactam group. An interim efficacy analysis will be conducted at 223 patients per group (446 total). If the *p*-value for a test of no difference was <0.005 then the trial would stop at that time. Otherwise, the trial will continue enrolling patients until 445 patients per group have been accrued, for a total of 890 patients overall. At the final analysis, the null hypothesis of no difference between groups will be rejected if the p-value for the test was <0.048. The study is expected to be completed within 24 months. All analyses will be conducted among resected patients. For the primary endpoint, a logistic regression model will be fitted where the outcome is SSI yes or no, the primary predictor is the randomized treatment group, and additional adjustment is made for preoperative biliary stent presence. There are a number of secondary endpoints as well. For secondary endpoints, logistic regression models with the secondary endpoint as the outcome, randomization group as the primary predictor, and additional adjustment for preoperative biliary stent presence will be used.

Funding Sources	No external-not-for-profit funds are available for the conduct of this trial. Specifically, participating institutions must provide, at their own cost, the trial drugs (cefoxitin, piperacillin-tazobactam). The Americas Hepatopancreatobiliary Association (AHPBA) Clinical Trials Committee will provide material support for data analysis of this trial only. The American College of Surgeons will not provide additional funding for the conduct of this trial as the trial will be conducted using already-in-place processes at eligible and participating institutions.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

This study aims to compare the differences in surgical site infection (SSI) rates of patients who undergo pancreatoduodenectomy (PD) for any indication by the type of surgical antibiotic prophylaxis administered. This is a randomized, open-label, multi-institutional phase III therapeutic trial of cefoxitin vs. piperacillan-tazobactam in patients undergoing PD. Data collection processes are based on the ACS NSQIP framework and infrastructure. After randomization, patients will receive one dose of either cefoxitin or piperacillan-tazobactam within 1 hour of incision time, redosed every 2-4 hours in the

operating room until closure of the incision, and discontinued within 24 hours following anesthesia end time. Patients will be followed for determination of SSI occurrences for 30 days following their index operation, unless they withdraw their consent.

Primary Objective:
To compare the effectiveness of cefoxitin, a second generation cephalosporin (Cohort 1), with piperacillin-tazobactam, a broad-spectrum penicillin (Cohort 2), as surgical antibiotic prophylaxis in decreasing the overall rate of postoperative SSIs in patients undergoing PD. The primary endpoint, overall SSI rate, is defined as superficial incisional SSI, deep incisional SSI, or organ/space SSI within the first 30 days after the operation, as defined according to the ACS NSQIP data collection operations manual (Appendix A1 and A2).

Hypothesis: A broad-spectrum penicillin as surgical antibiotic prophylaxis, will result in lower rates of SSIs (i.e., superficial, deep incisional, and organ/space) within 30 days from the index operation as compared to a standard second generation cephalosporin.

Secondary Objective(s):
To measure and compare the occurrences of non-SSI morbidity and healthcare utilization occurring in patients given a second generation cephalosporin as surgical antibiotic prophylaxis (Cohort 1) versus a broad-spectrum penicillin (Cohort 2). Secondary endpoints will also be collected according to the ACS NSQIP data collection operations manual within the first 30 days following the operation (Appendix A1 and A2). Specifically, secondary endpoints related to non-SSI morbidity include pneumonia, intraoperative or postoperative unplanned intubation, intraoperative or postoperative pulmonary embolism, ventilator dependence over 48 hours, progressive renal insufficiency or acute renal failure requiring dialysis, urinary tract infection, intraoperative or postoperative stroke or cerebral vascular accident, intraoperative or postoperative cardiac arrest requiring CPR, intraoperative or postoperative myocardial infarction, intraoperative or postoperative transfusion of red blood cells, vein thrombosis requiring therapy, postoperative clostridium difficile colitis, sepsis, sepsis shock, pancreatic fistula, delayed gastric emptying, intraoperative drain management, need for percutaneous drain placement, and death during operation or postoperative death within 30 days of procedure. Secondary endpoints related to healthcare utilization include a hospital stay > 30 days, hospital readmission, and unplanned reoperation.

Hypothesis: Use of a broad-spectrum antibiotic will result in lower non-SSI morbidity and healthcare utilization rates as compared to a standard second generation cephalosporin.

Correlative Studies:
To determine the bacterial isolates and sensitivities of SSIs that occur in patients in both cohorts.

To determine the bacterial isolates and sensitivities of intraoperative bile cultures obtained from patients in both cohorts.

3.0 BACKGROUND AND RATIONALE

PANCREATODUODENECTOMY

The first successful pancreatoduodenectomy (PD) was performed as a two-stage procedure by Walter Kausch in 1909. Later, Allen O. Whipple popularized this procedure in a one-step procedure with a case series of 37 operations performed during his lifetime. A PD is performed for benign or malignant lesions in the periampullary region and involves an en bloc resection of the head of the pancreas, duodenum, proximal jejunum, gallbladder, and oftentimes the distal stomach with subsequent reconstruction of the alimentary tract.

Because of high mortality rates nearing 25% following PD, the operative approach was nearly abandoned in the 1970s. During the 1980s and 1990s, however, high-volume centers developed in which complex alimentary procedures were commonly performed and, as a result, the benchmark for operative mortality following PD in the current era is now below 5%.[1, 2]

Despite improving mortality rates due to improvements in patient selection, surgical technique, and perioperative care, the incidence of perioperative morbidity after PD remains high and ranges from 40% to 58%.[1, 3, 4] The most common postoperative complications from PD include delayed gastric emptying (15-20%), pancreatic fistula (10-20%), and surgical site infection (SSI) (11-48%). As the majority of PD procedures are performed for periampullary malignancies, such as pancreatic cancer, perioperative complications can significantly delay receipt of adjuvant chemotherapy potentially impacting cancer outcome and patient survival.[5-8]

3.2 AMERICAN COLLEGE OF SURGEONS NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM (ACS NSQIP)

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is a nationally validated, risk-adjusted, outcome-based approach to measure and improve surgical care. It employs a prospective data registry to quantify 30-day, risk-adjusted surgical outcomes, which provide a standardized comparison of outcomes among all hospitals in the program. ACS NSQIP has a rich history stemming from the mid-1990s.[9] Peer-reviewed studies have shown that ACS NSQIP is effective in improving the quality of surgical care and reducing complications, which lead to lower costs. In addition, collaborations with the federal government and collaboratives among participating hospitals have advanced ACS NSQIP effectiveness in surgical quality improvement.

More than 700 hospitals voluntarily participate in the ACS NSQIP to improve surgical care quality. Hospitals subscribing to the program are provided benchmarked performance reports on 30-day, risk-adjusted surgical outcomes in comparison to all hospitals in the program.[10,11] Trained data abstractors, called Surgical Clinical Reviewers (SCRs), at each hospital collect patient information pertaining to demographics, operative details, and postoperative outcomes from the clinical record using standardized definitions up to 30 days from the index operations. Outcomes are determined directly from the medical record, by communicating with any involved providers, or from the patient directly via mail or telephone. Operations are recorded using Common Procedural Terminology (CPT®) codes. While outpatient operations are included, minor operations in free-standing surgery centers or in offices are not. Submitted data are periodically

audited to ensure quality and reliability between abstractors.[12] All patient information submitted to the ACS NSQIP for quality improvement are de-identified and compliant with the Health Information Portability and Accountability Act (HIPAA) of 1996.

The ACS NSQIP offers three program options (Essentials, Procedure Targeted, Small & Rural) to their subscribing hospitals based upon the hospital's size, operative volume, and quality improvement goals. Hospitals that participate in the Procedure Targeted program can select from 34 different procedure types to "focus" their quality improvement efforts. For example, hospitals that participate in the Procedure Targeted Pancreatectomy program increase the number of pancreatectomies accrued into the ACS NSQIP registry (usually 100%) and collect additional procedure-specific details and outcomes (e.g., pancreatic fistula, delayed gastric emptying, etc.) to evaluate their performance on pancreatectomies.

While the central tenant of the ACS NSQIP is surgical quality improvement, it has served myriad other purposes. For example, secondary analyses of the rich data collected have also made considerable contributions to clinical practice and health policy. Furthermore, as a registry, it might also be ideal for conducting trials. To overcome some of the contemporary challenges facing traditional randomized controlled trials (RCTs), recent trialists have begun leveraging the abundance of clinical registries as platforms for conducting randomized trials. The registry-based randomized trial, or randomized registry trial (RRT), aims to approach the statistical rigor of randomization, while expediting patient enrollment, minimizing cost, and improving generalizability of findings.[13-17] This study represents the first RRT in surgery.

Through the ACS NSQIP, hospitals with similar quality improvement interests and focuses form collaboratives to network, share best practices, and learn from one another. The Hepato-Pancreato-Biliary (HPB) Collaborative, founded in late 2014, is one prominent example of a collaborative formed through the ACS NSQIP and currently comprises over 80 hospitals. Studies have demonstrated that collaboratives improve surgical quality, and statewide initiatives, such as those in Tennessee and Illinois, have formed using this framework.[18] Specific to this study, all hospitals participating in the ACS NSQIP HPB Collaborative will be eligible for participation as long as they agree to capture all PDs performed at their institution during the trial study period.

This pragmatic trial will utilize the ACS NSQIP for data collection according to ACS NSQIP standard operating procedures already in place at participating hospitals. The use of standard of care antibiotics will allow the trial to be conducted in a pragmatic and "standard of care" fashion with no extraneous data collection (except those data required to safely conduct the trial) or treatment. Among the many outcomes monitored and tracked through the ACS NSQIP (Appendix A1 and A2), surgical site infections (SSIs) have always been a primary focus to improve surgical quality. Hospital performance is benchmarked using SSI rates. Standardized definitions based upon the US Centers for Disease Control definitions are used (see below). Although SSI rates overall across all types of operations have decreased in hospitals in the ACS NSQIP, it appears that SSIs occurring after PD have remained high.[19]

3.3 SURGICAL SITE INFECTIONS BACKGROUND

SSIs remain the most common and costly of all hospital acquired infections (HAIs), accounting for nearly 20% of all HAIs.[20] SSIs are associated with increased length of stay (LOS) and a 2-to-11-fold increase in mortality. Though most patients recover from an SSI without long-term adverse sequelae, 77% of postoperative mortalities in patients with an SSI can be attributed to the infection itself.[20,21]

The financial burden of SSIs is considerable, ranking as the most costly of the HAIs. The annual cost of SSI in the United States is estimated at $3.5-10 billion.[21] Increased costs from SSIs are driven by increased LOS, emergency department visits, and readmission rates.[22] On average, a SSI extends hospital length of stay by 9.7 days, and increases the cost of hospitalization by over $20,000 per admission. Over 90,000 readmissions annually are attributed to SSI, costing an additional $700 million per year.[20,21,23,24] Because up to 60% of SSIs were estimated to be preventable with the use of evidence-based measures, the rate of SSIs has become a pay-for-performance metric, such as the Medicare Hospital Value-Based Purchasing program. Accordingly, the multiagency Surgical Care Improvement Project (SCIP) and the ACS NSQIP have emphasized reduction of SSIs in quality improvement efforts.[21,25-27]

The detection and diagnosis of a SSI depends on a standardized definition. The Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN) classification of SSIs is the most widely used (Figure 1).[28] This definition is used for research, quality improvement, public reporting, and pay-for-performance comparisons. According to this definition, SSIs are classified by depth and tissue spaces involved: (1) a superficial incisional SSI involves only the skin or subcutaneous tissue; (2) a deep incisional SSI involves the fascia and/or muscular layers; and (3) an organ/space SSI involves any part of the body opened or manipulated during a procedure excluding the previously mentioned layers. These definitions are also employed by the ACS NSQIP when identifying and tracking SSIs across their approximately 700 participating hospitals (see Appendix A1 and A2). Because an essential strength of the ACS NSQIP is standardized, audited data abstraction processes, SSIs are tracked with less variability and more reliability than methods required of NHSN.[29]

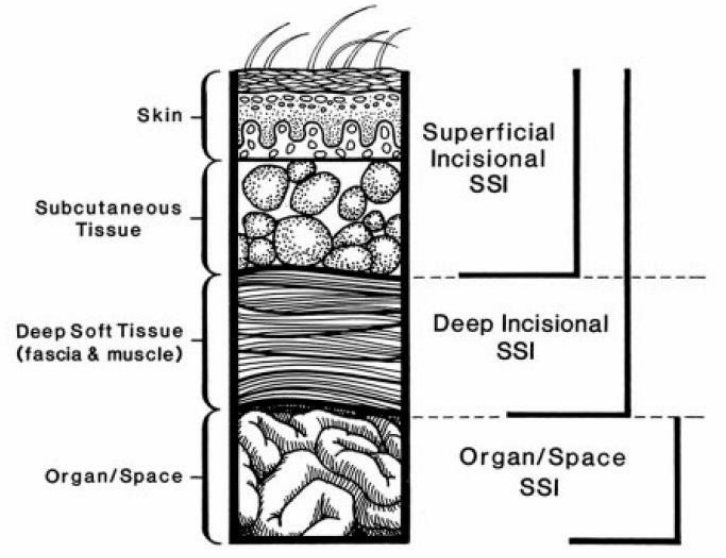


Figure 1. CDC classifications of surgical site infection [28].

To aid decision making for surgical antibiotic prophylaxis administration, a surgeon can preoperatively determine whether administration of antibiotic prophylaxis is appropriate based upon the expected microbial contamination of the operation, so-called wound classification.[28] Using this CDC wound classification schema, PD is categorized as either a clean-contaminated (Class II; in the absence of a preoperatively placed biliary stent) or a contaminated (Class III; in the presence of the stent or cholangitis) surgical wound.

3.4 SURGICAL SITE INFECTIONS AND PANCREATODUODENECTOMY

Despite rates of SSIs in other complex abdominal operations decreasing, the rate of SSIs after PD has remained unchanged, ranging from 11% to 48%.[4] An internal analysis of data from the approximately 70 institutions within the Hepato-Pancreato-Biliary (HPB) Collaborative of the ACS NSQIP detailing 3,592 PDs in 2015 revealed the rate of postoperative combined superficial incisional, deep incisional, and organ/space SSIs to be 21.7% (n = 778), nearly three-fold the rate seen after colon resections, which was 8.9% in ACS NSQIP hospitals from 2015. Factors associated with the high rate of SSIs in patients undergoing PD include preoperative biliary stenting, malnutrition, receipt of neoadjuvant therapy, and prolonged operative duration.[30,31]

Approximately 70% of patients present with obstructive jaundice due to malignant compression of the distal common bile duct from a periampullary tumor, particularly pancreatic cancer.[1] Frequently, these patients undergo biliary decompression with stent placement during endoscopic retrograde cholangiopancreatography (ERCP) to alleviate symptoms of hyperbilirubinemia, to correct coagulopathy, and to prevent development of ascending cholangitis and malnutrition. However, biliary decompression with a stent via ERCP results in free flow of intestinal contents into the normally steril biliary tree and results in biliary contamination with intestinal flora. Other logistical reasons for biliary stent placement include initial diagnosis by a gastroenterologist or as a bridge to surgical therapy (e.g., when neoadjuvant therapy is indicated for patients with borderline resectable disease).[31]

Common to all of these reported complications is a strong association between preoperative biliary drainage and postoperative SSIs.[23,32-34] Barreto et al. compared the characteristics of patients who underwent PD and developed SSIs compared to those who did not.[35] All patients were given ertapenem as surgical antibiotic prophylaxis. They found 4.6-times greater odds of SSI in those who had biliary stenting (95% confidence interval 2.0-10.4). However, one-third of those with SSIs in their study did not have biliary stenting. Similarly, Sahora et al. found a SSI rate of 19% in those with biliary stenting compared to 9% in those without (p = 0.001).[36] When they compared intraoperative bile cultures of stented patients with and without SSIs, they found the presence of *Enterobacter* spp. (OR 2.4, 95% CI 1.5-4.1) and *Citrobacter* spp. (OR 2.3, 95% CI 1.1-5.2) in the bile significantly increased the odds of a SSI. Cortes et al. performed a similar study in France where 79 patients undergoing PD for were given a first-generation cephalosporin (i.e., cefazolin) as the prophylactic antibiotic and intraoperative bile cultures were obtained.[37] Postoperative infectious complications were more common in the

cohort with culture-positive bile (65% vs. 37%, $p = 0.003$) and isolated microbes were resistant to cefazolin in 97%. Notably, 37% of patients had a SSI despite having culture-negative bile. More than 60% of the microorganisms isolated from SSI cultures were sensitive to piperacillin-tazobactam. Also in France, Sourrouille et al. prospectively examined 175 patients and found positive bile cultures in 81% of cases with preoperative biliary stenting.[38] When examining the sensitivities of the microorganisms isolated from SSIs, 0% were sensitive to a second-generation cephalosporin, while 90% were sensitive to piperacillin-tazobactam. Similarly, Gavazzi et al. reported positive bile cultures in 58.9% patients following preoperative biliary drainage before PD.[39] The reported incidence of SSI in that cohort was 20.8%. Limongelli et al. reported a SSI rate of 29% after PD, of which 69% occurred in patients who had preoperative biliary stenting.[40] Recently, Fong et al. retrospectively analyzed the microbiology of post-PD SSI cultures and their association with the choice of antibiotic prophylaxis from three high-volume institutions.[3,41] 1,623 patients underwent PD with a superficial SSI rate of 8.2% (n = 133); low as expected for those with superficial SSIs only. Preoperative biliary stenting was the strongest predictor of postoperative SSI (OR 2.5; 95% CI 1.58-3.88), and microbes isolated in intraoperative bile cultures were similar to those identified in the SSI cultures.

The costs of SSIs following PD have been evaluated by Enestvedt et al. in a single-institution trial at a high-volume academic center.[42] Additional hospital costs of a wound infection and intra-abdominal abscess in the postoperative period following PD were $18,184 and $46,166, respectively. Ceppa et al. examined the ACS NSQIP data of 895 hepatopancreatobiliary procedures at their institution and showed that increasing severity of SSI resulted in greater costs.[23] Notably, they showed that their reduction in SSI rates from 2007 to 2009 resulted in a cost savings of $11,462 per infection totaling approximately $370,000 in 2009.

3.5 SURGICAL CARE IMPROVEMENT PROJECT (SCIP) MEASURES

In 2003 the Centers for Medicare and Medicaid Services (CMS) initiated a program to reduce preventable surgical complications including SSIs.[27,43,44] This resulted in the creation of the Surgical Care Improvement Project (SCIP) measures.[21,28,45] The 3 SCIP measures with regard to antibiotics and SSI prevention include 1) administration of antibiotics within 1 hours of incision time, 2) selection of appropriate antibiotic therapy, and 3) discontinuation of antibiotics within 24 hours after surgery end time (or 48 hours for cardiac procedures). The antibiotic recommendations for gastrointestinal and biliary tract operations are summarized in Table 1. The current SCIP guidelines recommend a one-time dose of cefazolin (first generation of cephalosporin) of 2-3 grams given every 4 hours in patients with no evidence of β-lactam allergy as antimicrobial prophylaxis in PD. In patients with a contaminated biliary tree, as seen in preoperative placement of a biliary stent, cefazolin, cefoxitin (2 grams every 2 hours), cefotetan (second generation cephalosporins) (2 grams every 6 hours), or ceftriaxone (third generation cephalosporin) (2 grams once). Alternative agents in patients with a β-lactam allergy include clindamycin or vancomycin plus aminoglycoside or aztreonam or fluoroquinolone.

Table 1. Recommended antibiotics for surgical antibiotic prophylaxis.[45]

Type of Procedure	Recommended Agents	Alternative for β-lactam Allergy
Gastroduodenal		
Procedures involving entry into lumen of gastrointestinal tract (bariatric, pancreatoduodenectomy)	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Procedures without entry into gastrointestinal tract (antireflux, highly selective vagotomy) for high-risk patients	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract		
Open procedure	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone
Laparoscopic procedure		
Elective, low-risk	None	None
Elective, high-risk	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone Metronidazole + aminoglycoside or fluoroquinolone

3.6 SCIP MEASURES AND PANCREATODUODENECTOMY

It remains unknown whether the standard choice of SCIP recommended antimicrobial surgical prophylaxis (i.e., first or second generation cephalosporin) in patients undergoing PD is the most effective at reducing SSIs.[45-49] Observational studies in the United States, Europe, and Japan have suggested that a second generation cephalosporin may provide inadequate coverage for the microbes encountered during PD, especially in patients who have had preoperative biliary stenting. The most common isolates from SSIs following PD include the following: *Enterococcus* spp. (50-60%), *Escherichia coli* (30-40%), *Klebsiella* spp. (20-30%), *Enterobacter* (15-20%), and other organisms (10-15%). Due to both intrinsic and extrinsic resistance mechanisms *Enterococcus* spp is not appropriately covered by first, second, or third generation cephalosporins. In addition, although *Enterobacter* spp is appropriately covered by cephalosporins, a high rate of institutional resistance to ampillicin-sulbactam has rendered this regimen insufficient.

A small retrospective pilot study at UCLA compared the rate of SSI following PD when antimicrobial surgical prophylaxis was changed from the SCIP recommended cefoxitin (62%), cefazolin and metronidazole (15%), and clindamycin (8%) to a piperacillin-tazobactam regimen.[50] Antibiotics were redosed according to guidelines based on the half-life of the antibiotic. During the time period administrating the SCIP-recommended antibiotics, SSIs were 32.4 per 100 cases with *Enterobacter*

(50%) and *Enterococcus* (42%) the most common culture isolates. Following the change to the piperacillan-tazobactam regimen the SSI rate was 6.6 per 100 cases, *p*=0.004). A similar study by Kondo et al. examined their single-institution experience in 116 patients undergoing PD following a change from second-generation cephalosporin antimicrobial surgical prophylaxis to a regimen with piperacillan-tazobactam in β-lactam tolerant patients.[51] Following the change in antibiotic regimen, the incidence of SSI decreased from 46.6% to 24.1 (*p*=0.0116). In both studies, there was no significant difference in preoperative biliary stenting between the two antibiotic regimens. The efficacy of the piperacillan-tazobactam regimen in decreasing the rate of SSIs is not surprising, as this regimen is highly sensitive to all of the aforementioned common bacterial isolates in post-PD SSI.

Currently, based on reported case series on PD and SSI, the most common surgical antibiotic prophylaxis is a second-generation cephalosporin, which may be inadequate based upon the microorganisms isolated from SSI cultures. A summary of the studies is presented in Table 2.

3.7 INTRODUCTION OF INVESTIGATIONAL TREATMENTS AND OTHER STUDY TREATMENTS

3.7.1 Overview of cephalosporins

Cephalosporins, as a type of β-lactam antibiotic, inactivate the enzymes involved in bacterial cell wall synthesis and result in bactericidal activity. Clinically, they are frequently grouped into five “generations” based upon their spectrum of activity against aerobic, facultative gram-negative bacilli, and gram-positive bacteria.[52] The most commonly utilized cephalosporins for surgical antibiotic prophylaxis are first- and second-generation.[28,45-47]

Cefazolin is the only parenteral first-generation cephalosporin available in the United States, and is widely recommended and used for surgical antibiotic prophylaxis including pancreatic resections. Cefazolin has activity against the most common surgical-site microbes including methicillin-sensitive *S. aureus* and coagulase-negative staphylococci. However, for operations that involve entry into the lumen of the intestinal tract, such as in PD, cefazolin has limited to no activity against gram-negative bacilli.

Cefoxitin is a second-generation cephalosporin with broadened activity against *E. coli*, *Proteus* species, *Klebsiella* species, and many strains of *Bacteroides*. Notably, it has less activity against *Staphylococcus*. It is therefore more appropriate and recommended as surgical antibiotic prophylaxis for operations involving entry into the lumen of the intestinal tract, biliary operations, and vaginal operations. As prophylaxis, 2g of cefoxitin is administered 30-60 minutes prior to surgical incision followed by re-dosing of 2g every 2-4 hours while the incision is open, and for no longer than 24 hours after the incision is closed.[28,45]

Cefoxitin remains the only cephalosporin with antimicrobial activity suitable for gastrointestinal flora, specifically because of its activity against *Bacteroides fragilis* group. In addition to surgical antibiotic prophylaxis, cefoxitin is frequently used following penetrating trauma, uncomplicated acute appendicitis, perforated duodenal ulcers and other less severe intra-abdominal infections.

Adverse reactions to the cephalosporins are rare with the most common being diarrhea occurring 1-10% of the time. Severe life-threatening reactions occur <1% of the time. As a β-lactam, type I hypersensitivity reactions to cephalosporins can occur in 30% of patients with type I hypersensitivity reactions to penicillins.[53,54] However, 98% of penicillin skin test-positive patients are able to tolerate cephalosporins.[55] Among patients who report penicillin reactions but do not undergo testing, between 0.2 and 8% will react if given a cephalosporin.[53,56]

Table 2. Summary of observation studies examining surgical site infections and surgical antibiotic prophylaxis in PD.

Author(s), year	Country	Breadth	N	PBD Rate, %	SSI Rate, %	Surgical antibiotic prophylaxis (β-lactam tolerant)	Most common bacterial isolates from SSI
Barreto 2014 [35]	India	Single institution	277	39	13	Ertapenem	Not reported
Cortes 2006 [37]	France	Single institution	79	43	32	First-generation cephalosporin	*Enterococcus* spp., *E. coli*, and *Klebsiella* spp.
Donald 2013 [50]	USA	Single institution	176	30	32	First- or second-generation cephalosporin	*Enterobacter* spp., *Enterococcus* spp., coagulase-negative *Staphylococcus*
Fong 2016 [41]	USA, Italy	Multi-institution	1623	52	8*	First- or second-generation cephalosporin	*Enterococcus* spp., *Enterobacter* spp., *S. aureus*
Gavazzi 2016 [39]	Italy	Single institution	180	49	25	First-generation cephalosporin	*Enterococcus* spp., *E. coli*, *Klebsiella* spp.
Howard 2006 [33]	USA	Single institution	138	62	14	Second- or third-generation cephalosporin, ampicillin-sulbactam	*Enterococcus* spp., *Klebsiella* spp., yeast
Kent 2013 [2]	USA	Single institution	550	17	31	First-generation cephalosporin + metronidazole	*Staphylococcus* spp., *Enterococcus* spp., *E. coli*
Kondo 2013 [51]	Japan	Single institution	116	71	47	Second-generation cephalosporin	*Enterococcus* spp., *E. coli*, *Klebsiella* spp.
Limongelli 2007 [40]	UK	Single institution	220	46	45	Second-generation cephalosoporin + metronidazole	*Enterococcus* spp., lactose-fermenting coliform (e.g., *Enterobacteriaceae* spp.), non-lactose-fermenting coliform (e.g., *Pseudomonas* spp.)
Okano 2015 [57]	Japan	Multi-institution	4147	47	27	Second-generation cephalosporin	*Enterococcus* spp., *Enterobacter* spp., *Klebsiella* spp.
Sahora 2016 [36]	USA	Single institution	1000	50	24	Second-generation cephalosporin	*Enterococcus* spp., *Streptococcus* spp., *Klebsiella* spp
Sourrouille 2013 [38]	France	Single institution	175	57	21	Second-generation cephalosporin	*Enterococcus* spp., *E. coli*, *Klebsiella* spp.
Sudo 2014 [34]	Japan	Single institution	254	54	3*	First- or fourth-generation cephalosporin	*Enterococcus* spp., *Klebsiella* spp., *Enterobacter* spp.
Sugiura 2012 [58]	Japan	Single institution	408	59	51	First-generation cephalosporin	*Enterococcus* spp., *Enterobacter* spp., *Klebsiella* spp.

PBD: preoperative biliary drainage/stenting; SSI: surgical site infection; * superficial SSI only

3.7.2 Overview of piperacillin-tazobactam

Penicillins are another type of β-lactam antibiotic.[59,60] As such, they have antimicrobial properties against gram-positive bacteria. Gram-negative bacteria frequently produce β-lactamases, enzymes that degrade β-lactam antibiotics, and confer antibiotic resistance. β-lactamase inhibitors are frequently administered in combination with penicillins to extend the antimicrobial activity of penicillins. Examples of β-lactamase inhibitors include clavulanate, sulbactam, and tazobactam. Adding tazobactam to piperacillin extends the activity of piperacillin against *S. aureus, H. influenza, Neisseria gonorrhoeae,* some Enterobacteriaceae, and anaerobes. Most importantly, it has greater activity against streptococci and enterococci. Nevertheless, it does not provide coverage for methicillin-resistant staphylococci (e.g., methicillin-resistant *S. aureus* [MRSA]), strains of enterococci that are resistant to both β-lactams and aminoglycosides, and certain gram-negative bacilli, such as resistant strains of *Pseudomonas*. As surgical antibiotic prophylaxis, piperacillin-tazobactam is administered at a dose of 3.375-4.5 g within 60 minutes prior to surgery and readministered during the surgical procedure based on half-life.[28,45]

Serious adverse events from piperacillin-tazobactam are relatively infrequent.[60] Analysis of adverse events and laboratory tests performed during clinical trials revealed no unusual or unanticipated toxicity. Liver function tests may become abnormal, but these have almost always been transient and of little clinical consequence. Piperacillin-tazobactam possesses a safety profile characteristic of other β-lactam agents. Rates of reactions are comparable to those reported in the literature for piperacillin alone, ticarcillin-clavulanate, ampicillin-sulbactam, and imipenem-cilastatin. Among 1,111 patients enrolled in phase III trials of piperacillin-tazobactam, 174 (16%) had one or more adverse events, and this was no different compared to imipenem/cilastatin.[59,60] Drug-related gastrointestinal disturbances were most common, occurring in 4.6% of patients given piperacillin-tazobactam. Diarrhea is the most common side effect experienced by patients, but often it does not impede completion of therapy. Furthermore, it is relatively free of adverse effects in a variety of dosages and clinical settings. Clearance of piperacillin-tazobactam may be impaired in patients with advanced renal disease, but compensatory dosage adjustment guidelines are standard and not complicated. This study does not include patients with renal failure. Allergy may be a limiting factor, but it appears to occur no more commonly than with other β-lactam agents, including cephalosporins.[61]

3.8 STUDY RATIONALE

This study aims to leverage the ACS NSQIP data collection processes and infrastructure in collaboration with the AHPBA to prospectively compare two FDA approved antibiotics used as surgical antibiotic prophylaxis in patients undergoing PD. Specifically, this is a pragmatic, multi-center randomized controlled trial comparing the SCIP-recommended antimicrobial prophylaxis of a second generation cephalosporin, cefoxitin (which is FDA approved for use as a surgical antibiotic prophylaxis), with piperacillin-tazobactam (which is not FDA approved for surgical antibiotic prophylaxis, but is often used in this way off label) in patients undergoing elective PD. The scientific question and study design are attractive for the following reasons:

- Although the mortality rates following PD have decreased dramatically over the past three decades, perioperative morbidity rates remain high and are driven mainly by infectious complications from SSIs.
- The implementation of SCIP measures has influenced the culture of quality improvement; however, adherence to performance measures alone in the absence of randomized controlled trials demonstrating improvement in patient outcomes is insufficient and is contrary to the spirit of continuous quality improvement.
- Based upon abundant retrospective studies, institutional common bacterial isolates indicate that SCIP recommended antimicrobial prophylaxis with second generation cephalosporins does not adequately cover the organisms in SSIs occurring after PD.
- Administration of piperacillan-tazobactam in preliminary studies has demonstrated improved efficacy compared to SCIP recommended antimicrobial prophylaxis in patients undergoing PD irrespective of preoperative biliary stenting.
- For surgical quality improvement purposes, SSI rates are monitored and tracked as part of the ACS NSQIP in addition to many other relevant outcomes. Therefore, it is reasonable to utilize the ACS NSQIP quality improvement platform in collaboration with the AHPBA to assess the endpoints in this study.
- This study represents the first randomized registry trial (RRT) in surgery, and can serve as proof of concept for other RRTs in the future.

It is our primary hypothesis that the piperacillan-tazobactam regimen as antimicrobial prophylaxis will be associated with decreased rates of SSIs within 30 days compared to the SCIP-recommended antimicrobial prophylaxis with a second generation cephalosporin, cefoxitin, in patients undergoing elective PD for any indication.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a non-blinded, randomized, open-label, multi-institutional phase III therapeutic trial of cefoxitin vs. piperacillan-tazobactam as surgical antibiotic prophylaxis in patients undergoing elective PD for any indication.

4.2 Intervention

After informed consent and randomization, patients will receive one dose of either cefoxitin or piperacillin-tazobactam within 1 hour of incision time, redosed every 2-4 hours in the operating room until closure of the incision, and discontinued within 24 hours after anesthesia end time. The half-lives of piperacillan-tazobactam and cefoxitin are 0.7-1.2 hours and 0.7-1.1 hours, respectively, in adults with normal renal function; therefore, American Society of Health-System Pharmacists (ASHP) therapeutic guidelines[45] recommend redosing antibiotics two times the half life, or every 2-4 hours for both antibiotics until skin closure. Surgical antibiotic prophylaxis must be discontinued within 24 hours after anesthesia end time according to the

same guidelines. Patients will be followed for determination of SSI occurrences for 30 days following their index operation, unless they withdraw their consent, using the ACS NSQIP standard operating procedures.

4.3 Correlative Studies

4.3.1 Postoperative SSI bacterial cultures

Investigators will be encouraged to collect bacterial cultures and isolates obtained from postoperative SSIs whenever feasible. These data will not be collected by the standard ACS NSQIP mechanism, but instead will be studied in a retrospective fashion by participating institutions where surgeons routinely perform these cultures via chart review. Specifically, these correlative studies will be performed by institutions whose surgeons routinely culture bile and/or their postoperative SSIs.

4.3.2 Intraoperative bile bacterial cultures

Investigators will be encouraged to collect bacterial cultures obtained intraoperatively from the biliary system in patients undergoing PD at the time of biliary duct transection whenever feasible. These data will not be collected by the standard ACS NSQIP mechanism, but instead will be studied in a retrospective fashion from institutions where surgeons routinely perform these cultures via chart review.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Each participating institution will supply the therapeutic drugs, cefoxitin and piperacillin-tazobactam, as part of institutional standard processes. No additional special instructions for maintaining, tracking, and monitoring of the therapeutic agents is necessary as part of this study and will be dependent on each participating institution's standard processes, such as pharmacy oversight, antimicrobial stewardship program, etc. These agents are currently used in practice and are neither novel nor require additional approval from regulatory bodies for use in this study's capacity. See Section 3.6 for additional details regarding each individual agent.

In the rare event of national drug shortages affecting the therapeutic agents used in this trial, we will substitute cefoxitin (Mefoxin®) for cefotetan (Cefotan®).[62] In this rare event, a dose of 2 g administered within 60 minutes prior to skin incision will be administered. Doses are not adjusted for weight. Following the ASHP Clinical Guidelines,[45] cefotetan, if used, will be redosed at 2 g every 6 hours until the skin incision is closed. The duration of cefotetan administration after incision close will be at the discretion of the treating surgeon as long as the antibiotic prophylaxis is discontinued, according to guidelines, within 24 hours of anesthesia end time. Continuation of cefotetan for longer than 24 hours as prophylactic purpose will constitute a protocol violation. However, administration of antibiotics postoperatively for non-prophylactic purposes (e.g. treatment for infection) should not be considered a protocol deviation. The time of administration and composition of the solvent will be at the discretion of the participating institution.

National drug shortages for piperacillin-tazobactam (Zosyn®) are incredibly rare. Because there are no other available drugs of the same class with the same antimicrobial properties,

there will be no substitution for piperacillin-tazobactam in the event of a national shortage. In this circumstance, patient accrual will be halted until appropriate supplies can be obtained.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered and enrolled to the study. Randomization of the patient to one of the two treatment arms may not occur until a subject is registered (see Section 15.0).

6.1 Subject Inclusion Criteria

- Age ≥ 18 years
- Patients undergoing elective pancreatoduodenectomy (PD) for any diagnosis/indication

6.2 Subject Exclusion Criteria

- Patients undergoing a minimally invasive PD, such as laparoscopic or robotic PD
- Patients with known and documented allergies to any of the penicillins, cephalosporins, or β-lactamase inhibitors
- Patients who are otherwise ineligible to receive the antibiotics in this study
- Patients highly unlikely to undergo PD according to the surgeon's judgment, such as conditions amenable to pancreas enucleation, ampullectomy, etc.
- Patients with long-term glucocorticosteroid use. The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
- Patients unable to provide informed consent
- Creatinine clearance (CrCl) ≤ 40 mL/min
- Patients receiving hemodialysis or peritoneal dialysis
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
- Patients with a known bacterial infection present at the time of surgery or who received antimicrobial therapy within 7 days prior to surgery

7.0 RECRUITMENT PLAN

The study will be open to all patients seen at the participating (ACS NSQIP) Hepato-Pancreato-Biliary (HPB) Collaborative institutions who meet the eligibility criteria outlined in Section 6.0. Furthermore, to be a participating institution, the institution must be part of the ACS NSQIP Procedure Targeted Pancreatectomy program and agree to collect all PDs performed at their institution during the study period.

Patients will be identified from surgical clinics for treatment of their disease. After a discussion of the patient's disease and a formulation of the initial treatment plan, the physician-investigator will describe the study to the patient. The protocol will be discussed in a private clinic room or office. Details including the risks and obligations of the subjects will be explained. For non-English speaking patients, an independent translator will be available

to communicate the details of the protocol. A research coordinator or appropriate designee will be available either in the clinic or by phone to answer any additional questions.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. The registration procedure will be conducted as described above. Patients will not receive payment for their participation on this study.

8.0 PRETREATMENT EVALUATION

Following determination of patient eligibility, patients will undergo preparations for PD according to the operating surgeon's standard of practice. No specific laboratory or radiologic examinations are necessary for this study beyond standard of practice.

9.0 TREATMENT/INTERVENTION PLAN

9.1 OVERVIEW

Study subjects who agree and are eligible to participate in this study will sign an informed consent at the time the treating surgeon recommends PD for their medical condition. Once informed consent is obtained and all eligibility criteria are met as detailed in Section 6.0, patients will undergo PD at the discretion of the treating surgeon.

9.2 STUDY TREATMENT

For this study, the term "study treatment" refers to either cefoxitin or piperacillan-tazobactam administered as surgical antibiotic prophylaxis. The procedure, pancreatoduodenectomy (PD), is standard of care for both benign and malignant conditions of the periampullary region (i.e., the area around and including the head of the pancreas).

Cefoxitin or piperacillan-tazobactam are drug products, administrated intravenously, and supplied by each participating institution. The trial drugs, cefoxitin and piperacillin-tazobactam, will be supplied by each participating institution and no external-not-for-profit funding will be used to obtain these trial drugs for participating institutions. Storage conditions are standard and described in the medication labels. PD will be performed in usual standard of care practice by the treating surgeon as described in Section 9.5.

Administration and dosing are based on published national guidelines, specifically those of the American Society of Health-System Pharmacists (ASHP).[28,45] As a pragmatic trial, the administration and dosing are also based upon currently in-place measures as defined by the SCIP and the US CDC on surgical antibiotic prophylaxis.[21,28]

9.3 CEFOXITIN ADMINISTRATION SCHEDULE AND DOSE ADJUSTMENT

Cefoxitin will be administered intravenously within 60 minutes (1 hour) of incision of the PD. Doses are not adjusted based on weight. No adjustments are necessary based upon renal function (i.e., glomerular filtration rate [GFR]) as patients requiring

dialysis are excluded. Cefoxitin will be re-administered during the operation every 120-240 minutes (2 hours) up to 3 doses until close of incision. For cases >12 hours, cefoxitin should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 6 hours until end of surgery. As a pragmatic trial, the duration of cefoxitin administration after incision close will be at the discretion of the treating surgeon as long as the antibiotic prophylaxis is discontinued, according to guidelines, within 24 hours of anesthesia end time. Continuation of cefoxitin for longer than 24 hours as prophylactic purpose will constitute a protocol violation. However, administration of antibiotics postoperatively for non-prophylactic purposes (e.g. treatment for infection) should not be considered a protocol violation. The time of administration and composition of the solvent will be at the discretion of the participating institution.

In the rare event of national drug shortages affecting the therapeutic agents used in this trial, we will substitute cefoxitin (Mefoxin®) for cefotetan (Cefotan®).[62] In this rare event, a dose of 2 g administered within 60 minutes prior to skin incision will be administered. Doses are not adjusted for weight. Following the ASHP Clinical Guidelines,[45] cefotetan, if used, will be redosed at 2 g every 6 hours until the skin incision is closed. The duration of cefotetan administration after incision close will be at the discretion of the treating surgeon as long as the antibiotic prophylaxis is discontinued, according to guidelines, within 24 hours of anesthesia end time. Continuation of cefotetan for longer than 24 hours as prophylactic purpose will constitute a protocol violation. However, administration of antibiotics postoperatively for non-prophylactic purposes (e.g. treatment for infection) should not be considered a protocol violation. The time of administration and composition of the solvent will be at the discretion of the participating institution.

9.4 PIPERACILLAN-TAZOBACTAM ADMINISTRATION SCHEDULE AND DOSE ADJUSTMENT

A single dose of 3.375-4.5 gm of piperacillan-tazobactam will be given intravenously within 60 minutes (1 hour) of incision of the PD. Additional doses of 3.375-4.5 grams of piperacillan-tazobactam will be given every 120-240 minutes (2-4 hours) until closure of skin incision following national guidelines.[45] **For centers that employ 3.375 gm doses of IV piperacillin-tazobactam:** Piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses. For cases > 12 hours, piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 6 hours until end of surgery. **For centers that employ 4.5 gm doses of IV piperacillin-tazobactam:** Piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses. For cases > 12 hours, piperacillin-tazobactam should be re-dosed every 120-240 minutes (2-4 hours) for up to 3 doses, then every 8 hours until end of surgery. As a pragmatic trial, the duration of piperacillin-tazobactam administration after incision close will be at the discretion of the treating surgeon as long as the antibiotic prophylaxis is discontinued, according to guidelines, within 24 hours of anesthesia end time. Continuation of piperacillin-tazobactam for longer than 24 hours as prophylactic purpose will constitute a protocol violation. However, administration of antibiotics postoperatively for non-prophylactic purposes (e.g. treatment for infection) should not be considered a protocol violation. The time of administration and composition of the solvent will be at the discretion of the participating institution. There will be no adjustment of dosage. Note specifically that doses of 3.375 and 4.5 grams are allowed in this protocol because these two dosages have equivalent concentrations and pharmacokinetics are similar (see Appendix C).

National drug shortages for piperacillin-tazobactam (Zosyn®) are incredibly rare. Because there are no other available drugs of the same class with the same antimicrobial properties, there will be no substitution for piperacillin-tazobactam in the event of a national shortage. In this circumstance, patient accrual will be halted until appropriate supplies can be obtained.

9.5 PANCREATODUODENECTOMY

Pancreatoduodenectomy is considered standard of care for benign and malignant conditions of the periampullary anatomical region (i.e., the area around and including the head of the pancreas). Following determination of patient eligibility, patients will undergo PD according to the operating surgeon's standard of practice. The perioperative care provided to both study treatment groups, including hair removal technique and skin preparation, will follow the standard practice of the operating surgeon in accordance with any standard operating procedures of the institution. Type of surgical incision, intraoperative use of sponges to contain contamination, glove and instant changes and saline irrigation of the surgical site, use and management of surgical drains, and closure of the incision at the end of surgery will be administered according to the preference of the surgeon. Additionally, use of wound protectors, topical antibiotics, and external wound vacuum dressings will be at the discretion of the surgeon. Use of nasogastric, gastrostomy or jejunostomy tubes as well as enteral or parenteral nutrition also will be at the discretion of the surgeon. Surgical antimicrobial prophylaxis will be continued following closure of the incision at the discretion of the treating surgeon so long as the antimicrobial prophylaxis is discontinued according to guidelines within 24 hours of anesthesia end time.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 SCREENING/PREOPERATIVE PHASE

Patients must provide a signed informed consent prior to any study-specific evaluations including screening. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 6.0. Patients must meet all eligibility criteria to be considered for enrollment in the study. All screening procedures must be performed within 21 days prior to PD unless otherwise stated. All data will be collected as part of American College of Surgeon National Surgical Quality Improvement Program (ACS NSQIP) by trained data collectors according to standard operating procedures and definitions (see Section 3 for description; Appendix A1 and A2 for data collection definitions).

10.1.1 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics prior to PD include:

- Date of birth
- Gender
- Race
- Hispanic ethnicity
- Preferred language
- Hospital admission date
- Operation date
- Common Procedural Terminology (CPT) code for operation

- In/Out patient status
- Origin status
- Principal anesthetic technique
- Surgeon specialty
- Surgeon National Provider Identification (NPI) number
- Height
- Weight
- Diabetes mellitus requiring therapy with non-insulin agents or insulin
- Current smoker within one year of operation
- Dyspnea
- Functional health status
- Ventilator dependent
- Chronic obstructive pulmonary disease (COPD)
- Ascites within 30 days prior to surgery
- Congestive heart failure (CHF) within 30 days prior to surgery
- Hypertension requiring medication
- Acute renal failure
- Currently requiring or on dialysis
- Disseminated cancer
- Open wound (with or without infection)
- Steroid/Immunosuppressant use for a chronic condition
- >10% loss of body weight in the 6 months prior to surgery
- Bleeding disorders
- Blood transfusions within 72 hours prior to surgery start time
- Sepsis within 48 hours prior to surgery
- Preoperative laboratory values (within 90 days of the operation)
    - Serum sodium
    - Blood urea nitrogen
    - Serum creatinine
    - Albumin
    - Total bilirubin
    - Aspartate transaminase (AST)/serum glutamin-oxaloacetic transaminase (SGOT)
    - Alkpaline phosphatase
    - White blood cell count (WBC)
    - Hematocrit
    - Platelets
    - International normalized ratio (INR)
    - Partial Thromboplastin Time (PTT)
- American Society of Anesthesiology (ASA) Classification
- Presence of preoperative jaundice
- Presence of a preoperative biliary stent
- Receipt of chemotherapy within 90 days of the operation
- Receipt of radiation therapy within 90 days of the operation

10.2 TREATMENT PHASE

Patients will be randomized after informed consent to either receive cefoxitin or piperacillan-tazobactam according to the following process:

After informed consent is obtained, patients will be randomized 1:1 and stratified based upon preoperative biliary stent presence. Site investigators will contact the trial coordinating center for randomization (see Section 14.0 for details). Randomization will occur before the day of the operation (see Section 15.2 for details).

Following randomization and administration of the assigned surgical antibiotic prophylaxis, the following perioperative data will be collected according to standard ACS NSQIP operating procedures and definitions (see Appendices A1 and A2 for additional details):

- Emergency operation status
- Wound classification
- Surgical wound closure
- Operation start and end times
- Additional operations/procedures performed simultaneously on the same patient
- Need for intraoperative blood transfusion within 72 hours of surgery start time
- Operative approach
- Type of surgical incision
- Use of a wound protector
- Pancreatic duct size at the time of the operation
- Pancreatic gland texture at the time of the operation
- Type of pancreatic reconstruction performed, if any
- Presence and type, if appropriate, of surgical drains
- If surgical drains are placed, whether they are placed to suction
- Need for vascular resection

10.3 POSTOPERATIVE PHASE

Following PD and administration of the assigned surgical antibiotic prophylaxis, patients will be followed for 30 days. The following data will be collected during this time period according to standard ACS NSQIP operating procedures and definitions (details in Section 12.0; Appendices A1 and A2):

- Superficial incisional surgical site infection (SSI)
- Deep incisional SSI
- Organ/space SSI
- Wound disruption
- Pneumonia
- Intraoperative or postoperative unplanned intubation
- Intraoperative or postoperative pulmonary embolism
- On ventilator >48 hours
- Progressive renal insufficiency
- Acute renal failure requiring dialysis
- Urinary tract infection
- Intraoperative or postoperative stroke/cerebral vascular accident (CVA)
- Intraoperative or postoperative cardiac arrest requiring CPR
- Intraoperative or postoperative myocardial infarction
- Venous thrombosis requiring therapy
- Sepsis
- *Clostridium difficile* infection
- Need for postoperative blood transfusion within 72 hours of surgery start time

- Acute hospital discharge date
- Hospital discharge destination
- Death during operation or postoperative death within 30 days of procedure
- Date of death
- Hospital readmission
- Unplanned reoperation
- Drain amylase, specifically on postoperative day #1 and highest drain amylase from postoperative days #2-30, if surgical drain was placed at the time of the operation, and still present for drain amylase level assessment
- Date of removal of last surgical drain, if surgical drain(s) placed at the time of the operation
- Presence of pancreatic fistula
- Presence of delayed gastric emptying
- Placement of percutaneous drain
- Malignancy versus benign pathology
- If malignant, pathologic American Joint Committee on Cancer stage
- If benign, tumor size

For the purposes of this study, the ACS NSQIP must collect additional data to ensure patient safety and the integrity of this study. These are listed below and additional details can be found in Appendix A3:

- Whether the patient is a participant in this study
- To which treatment arm the patient was randomized
- The type of protocol violation, if any
- Grade of drug reaction due to the therapeutic treatment, if any

ACS NSQIP will provide additional fields for these data to be stored in the same database that will house all other data collected for this study.

11.0 TOXICITIES/SIDE EFFECTS

Measures taken to ensure the safety of patients participating in this trial are based upon routine monitoring at each participating institution for drug reactions. Specifically, patients enrolled in this study will be evaluated by the study team at each participating institution clinically after administration of the therapeutic drugs, cefoxitin or piperacillin-tazobactam, as surgical antibiotic prophylaxis. Because the drugs of study are currently routinely and widely used, we do not anticipate uncovering additional adverse events beyond those already known of cefoxitin and piperacillin-tazobactam.

11.1 CEFOXITIN TOXICITY

11.1.1 Significant Adverse Reactions

1% to 10%: Gastrointestinal: Diarrhea

<1% (Limited to important or life-threatening): Anaphylaxis, angioedema, bone marrow depression, dyspnea, eosinophilia, exacerbation of myasthenia gravis, exfoliative dermatitis, fever, hemolytic anemia, hypotension, increased blood urea nitrogen, increased serum creatinine, increased serum transaminases, interstitial nephritis, jaundice, leukopenia, nausea, nephrotoxicity (increased; with aminoglycosides), phlebitis, prolonged prothrombin time, pruritus,

pseudomembranous colitis, skin rash, thrombocytopenia, thrombophlebitis, toxic epidermal necrolysis, urticaria, vomiting

11.1.2 Other Adverse Reactions

Hypersensitivity: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria). If a hypersensitivity reaction occurs, discontinue immediately.

Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months after antibiotic treatment.

GI disease: Use with caution in patients with a history of gastrointestinal disease, particularly colitis.

Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Elderly population: cefoxitin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function; use care in dose selection and monitor renal function.

11.2 PIPERACILLIN-TAZOBACTAM TOXICITY

11.2.1 Significant Adverse Reactions

Cardiovascular: Phlebitis (1%), flushing (≤1%), hypotension (≤1%), thrombophlebitis (≤1%)

Central nervous system: Headache (8%), insomnia (7%), rigors (≤1%)

Dermatologic: Skin rash (4%), pruritus (3%), purpura (≤1%)

Endocrine & metabolic: Hypoglycemia (≤1%), decreased serum albumin, decreased serum glucose, decreased serum total protein, electrolyte disturbance (increases and decreases in sodium, potassium, and calcium), hyperglycemia, hypokalemia, increased gamma-glutamyl transferase

Gastrointestinal: Diarrhea (11%), constipation (8%), nausea (7%), dyspepsia (3%), vomiting (3%), abdominal pain (1%), pseudomembranous colitis (≤1%)

Hematologic & oncologic: Decreased hematocrit, decreased hemoglobin, eosinophilia, leukopenia, neutropenia, positive direct Coombs test, prolonged bleeding time, prolonged partial thromboplastin time, prolonged prothrombin time, thrombocythemia, thrombocytopenia

Hepatic: Increased serum alkaline phosphatase, increased serum ALT, increased serum AST, increased serum bilirubin

Hypersensitivity: Anaphylaxis (≤1%)

Infection: Candidiasis (2%)

Local: Injection site reaction (≤1%)

Neuromuscular & skeletal: Arthralgia (≤1%), myalgia (≤1%)

Renal: Increased blood urea nitrogen, increased serum creatinine

Respiratory: Epistaxis (≤1%)

<1%, postmarketing, and/or case reports (Limited to important and life-threatening): Acute generalized exanthemous pustulosis, agranulocytosis, Clostridium difficile associated diarrhea, convulsions, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, eosinophilic pneumonitis, erythema multiforme, exfoliative dermatitis, hemolytic anemia, hypersensitivity reaction, jaundice, pancytopenia, shock, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

11.2.2 Other Adverse Reactions

Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (e.g., anaphylaxis, angioedema, urticaria).

Dermatologic effects: Serious skin reactions, including TEN and SJS, acute exanthematous pustulosis, and DRESS have been reported. If a skin rash develops, monitor closely. Discontinue if lesions progress.

Electrolyte abnormalities: Sodium content (2.84 mEq per gram of piperacillin) should be considered in patients requiring sodium restriction. Assess electrolytes periodically in patients with low potassium reserves, especially those receiving cytotoxic therapy or diuretics.

Hematologic effects: Prothrombin time, platelet aggregation, and clotting time abnormalities have been reported with piperacillin and particularly in patients with renal impairment. Discontinue if thrombocytopenia or bleeding occurs. Leukopenia/neutropenia may occur; appears to be reversible and most frequently associated with prolonged administration. Assess hematologic parameters periodically, especially with prolonged (≥21 days) use.

Superinfection: Use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months after antibiotic treatment.

Cystic fibrosis: An increased frequency of fever and rash has been reported in patients with cystic fibrosis receiving piperacillin.

Renal impairment: Use with caution in patients with renal impairment or underdeveloped kidneys; due to sodium load and to the adverse effects of high serum concentrations of penicillins.

Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 AMERICAN COLLEGE OF SURGEONS NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM (ACS NSQIP)

The American College of Surgeon National Surgical Quality Improvement Program (ACS NSQIP) is a nationally validated program that measures risk-adjusted surgical outcomes from participating hospitals to benchmark performance in the name of improving the surgical care provided to patients. This quality improvement program collects prospective, standardized, clinically meaningful data to assess outcomes. ACS NSQIP has a rich history and currently has more than 700 participating hospitals both nationally and internationally. Peer-reviewed studies have shown ACS NSQIP is effective at improving the quality of surgical care and reducing complications thereby leading to lower costs.[19] Because the study institutions participate in the ACS NSQIP and because the primary outcome is one central to surgical quality improvement, this study will utilize the standard operating procedures of the ACS NSQIP to assess its primary and secondary outcomes. Again, only patients treated at institutions participating in the ACS NSQIP, active in the ACS NSQIP HPB Collaborative, subscribe to the Procedure Targeted Pancreatectomy program option, and agree to accrue all 100% of their institution's PDs into the ACS NSQIP will be eligible for this study. This will ensure that the measurement of outcomes at all institutions participating in this study is standardized and consistent thereby preserving the integrity of this study. See Section 3.2 for other details.

12.2 DEFINITION OF OUTCOMES

Primary and secondary outcomes will be measured in this study using ACS NSQIP standard operating procedures and definitions. This ensures that the measurement of primary and secondary outcomes is consistent between each participating institution. The following reproduce a selection of the current definitions employed by the ACS NSQIP to monitor only this study's primary and secondary outcomes. Additional details and definitions may be found within Appendices A1 and A2.

The primary endpoint of this study is overall SSI rate, defined, according to the ACS NSQIP, as a composite of superficial SSI, deep incisional SSI, and organ/space SSI.

12.2.1 Superficial Surgical Site Infection

Superficial incisional surgical site infection (SSI) is an infection that involves only skin or subcutaneous tissue of the surgical incision.

An infection occurs within 30 days after the index operation and the infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

a. Purulent drainage, with or without laboratory confirmation, from the superficial incision; or,

b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; or,

c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision that is deliberately opened by the surgeon, unless incision is culture negative; or

d. Diagnosis of superficial incisional SSI by the surgeon or attending physician

12.2.2 Deep Incisional SSI

Deep incisional SSI is an infection which involves deep soft tissues. Deep soft tissues are typically any tissue beneath skin and immediate subcutaneous fat, for example, fascial and muscle layers.

It is an infection that occurs at the surgical site within 30 days after the principal operative procedure and involves deep soft tissues and at least one of the following:

a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site

b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38.0° C, localized pain, or tenderness, unless the site is culture-negative

c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination

d. Diagnosis of a deep incision SSI by a surgeon or attending physician

12.2.3 Organ/Space SSI

Organ/space SSI is an infection that involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation.

It is an infection that occurs within 30 days after the principal operative procedure and involves any of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during the operation and at least one of the following:

a. Purulent drainage from a drain that is placed through a stab wound into the organ/space. This does not apply to drains placed during the principal operative procedure, which are continually in place, with continual evidence of drainage/infection since the time of the principal operative procedure

b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space

c. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination

d. Diagnosis of an organ/space SSI by a surgeon or attending physician

12.2.4 Secondary Endpoints

Secondary endpoints based on the ACS NSQIP data include the following: pneumonia, intraoperative or postoperative unplanned intubation, intraoperative or postoperative pulmonary embolism, ventilator dependence over 48 hours, progressive renal insufficiency or acute renal failure requiring dialysis, urinary tract infection, intraoperative or postoperative stroke or cerebral vascular accident, intraoperative or postoperative cardiac arrest requiring CPR, intraoperative or postoperative myocardial infarction, intraoperative or postoperative transfusion of red blood cells, vein thrombosis requiring therapy, postoperative clostridium difficile colitis, sepsis, sepsis shock, pancreatic fistula, delayed gastric emptying, intraoperative drain management, need for percutaneous drain placement, withdrawal of care, death during operation or postoperative death within 30 days of procedure, hospital stay > 30 days, hospital readmission, and unplanned reoperation. . All of these outcomes are assessed within 30 days after the PD. Please see Appendix A1 and A2 for more details.

Correlative studies will be conducted on bacterial isolates from any SSIs that do occur and from routine intraoperative bile duct cultures. Specifically, these data include whether bacterial cultures were positive, and if positive, which bacterial species are present and their antibiotic sensitivities. These correlative studies are not collected by the ACS NSQIP mechanism, and thus will be conducted retrospectively via chart review at participating institutions that routinely collect these data.

13.0 CRITERIA FOR REMOVAL FROM STUDY

1. If prior to the administration of either therapeutic agent, the patient experiences a severe adverse event related to the anesthetic and does not undergo the planned PD
2. If prior to the administration of either therapeutic agent, the patient no longer has the capacity to make medical decisions
3. If, at any time, protocol ineligibility is identified, as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study
4. If, at any time, progressive disease is found and the planned operation, pancreatoduodenectomy, does not occur (e.g., metastatic disease at the time of operation requiring aborting the procedure)
5. Determination by the investigator that it is no longer safe for the subject to continue therapy
6. Changes in a patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator

If a patient is removed from the study before undergoing and receiving study drug, safety monitoring will end on the date the patient is taken off study.

14.0 BIOSTATISTICS

The primary aim of this study is to determine if administration of piperacillin-tazobactam as surgical antibiotic prophylaxis results in decreased rates of surgical site infection (SSI) as compared to the administration of cefoxitin. To accomplish this aim, patients undergoing elective pancreatoduodenectomy will be randomized to receive one of the two treatments and then will be followed for SSI occurrence for 30 days. Interest is in detecting a reduction in SSI rate from 0.20 in the cefoxitin group to 0.13 in the piperacillin-tazobactam group. An internal analysis of data from the approximately 70 institutions within the Hepato-Pancreato-Biliary (HPB) Collaborative of the ACS NSQIP detailing 3,592 PDs in 2015 revealed the rate of postoperative combined superficial incisional, deep incisional, and organ/space SSIs to be 21.7% (n = 778). Additional internal analysis of ACS NSQIP data that included additional hospitals revealed the overall SSI rate to be 20.4%. Therefore, these data represent the basis for the baseline rate of 20% used in this trial. The alternative rate of 13% represents a clinically meaningful reduction in SSIs in this patient population. This study will use a two-sided type I error rate of 0.05 and a power of 0.8. There will be one planned interim analysis when half of the patients have been accrued. The interim analysis is based on the O'Brien-Fleming spending function. We will accrue 223 patients per group for a total of 446 patients in total for interim analysis. At interim analysis, we would reject the null hypothesis of no difference between groups if the p-value for the test was <0.005, and the trial would stop at that time. Otherwise, the trial will continue enrolling patients until 445 patients per group have been accrued, for a total of 890 patients overall. At the final analysis, we would reject the null hypothesis of no difference between groups if the p-value for the test was <0.048.

The planned sample size of 890 is for resectable patients. Randomization is done pre-surgery but it is expected that approximately 10% of patients who are taken to the operating room will be deemed unresectable. These patients will be ineligible. Enrollment will continue until the planned sample size has been reached. In 2015, 2,210 pancreatoduodenectomies were conducted at 48 institutions where HPB surgeons have expressed interest in participating and meet this study's eligibility criteria. Accounting for recruitment and eligibility considerations, we expect to be able to complete the study within 24 months.

All analyses will be conducted among resected patients. This is an intention-to-treat analysis, such that all patients deemed eligible who undergo PD will be analyzed in the treatment arm to which they were randomized. If a patient who underwent treatment and PD dies or is lost to follow-up within 30 days of their surgery, this patient will count as a failure toward the primary endpoint, though the rate of such losses to follow-up is expected to be very low (~1-2%). For the primary endpoint, we will fit a logistic regression model where the outcome is SSI yes or no, the primary predictor is the randomized treatment group, and additional adjustment is made for preoperative biliary stent presence.

There are a number of secondary endpoints as well. All secondary endpoints are binary and will be analyzed using logistic regression models with the secondary endpoint as the outcome, randomization group as the primary predictor, and adjustment for preoperative biliary stent presence.

Finally, there are several exploratory objectives. Data will be collected on intraoperative bacterial cultures and isolates from the cut-edge of the biliary tree, and from any SSIs that occur postoperatively. These bacterial cultures and isolates from certain participating institutions will be summarized. Specifically, these data include whether bacterial cultures were positive, and if positive, which bacterial species are present and their antibiotic sensitivities. This will allow us to determine whether the type of antibiotic given as surgical antibiotic prophylaxis correlates with intraoperatively obtained bile cultures and SSIs that occurred.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

MSKCC ONLY

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.
Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

Research participant registration at the Participating Institutions is described in Appendix D, Multicenter Therapeutic Protocol Addendum.

15.2 Randomization

Patients will be randomized 1:1 to cefoxitin or piperacillin-tazobactam for prophylactic management of surgical site infection. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trials Management System (CTMS) and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and patients will be stratified by preoperative biliary stent presence. Randomization will occur prior to the day of surgery to ensure availability of institutional antibiotic.

For participating institutions other than MSKCC, randomization will be conducted using the same method for MSKCC patients as noted above. Confirmation of the randomization assignment, along with the participant ID will be sent by the MSKCC study coordinator via e-mail to the participating site study coordinator and the site Principal Investigator within 1 business day of receiving all completed required enrollment documents.

Randomization will only occur after all completed registration documentation is received by MSK. Due to the different timezones, randomization will only occur during the following timeframe:

Weekdays: Monday – Friday
Time: 9:00 AM – 5:00 PM Eastern Standard Time (EST)

16.0 DATA MANAGEMENT ISSUES

Data will be managed by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) as currently established at participating institutions. All data are managed at the ACS NSQIP in a de-identified fashion. No change to the current data management strategy as it exists between participating institution and the American College of Surgeons as specified under the Business Associate Agreements (BAAs)

between these entities will be necessary. Additional data that are not routinely collected by the ACS NSQIP are needed for the conduct of this trial. Please see Appendix A3 for details.

REDCap, Research Electronic Data Capture, is an open source platform that allows for the collection of research data in a secure manner over a web based interface. Usage of the platform is contingent on an open source license. The platform was developed by Vanderbilt University which MSK has a standing agreement with to allow the usage of REDCap for academic/research purposes.

For this protocol, REDCap will be only used as a notification platform. It will serve as a second notification to remind investigators of the randomization information. MSK study coordinator will email the following information to ACS: patient's first and last name (or first and last initials), MRN (or CTMS generated MRN), site/hospital, treating physician/surgeon, DOB (or birth month and year), date of treatment, treatment arm (randomization information). The ACS fellow will input this information in REDCap. The ACS fellow will be responsible for emailing the randomization reminders to the sites. An email will be sent to the investigators and the study staff a day prior to the patient's surgery date. If the email is sent and rescheduling of the surgery occurs, the investigator/staff will be able to notify the MSK staff via the link in the email notification. The non-MSK site is responsible for immediately notifying MSK staff of any surgery scheduling changes, even prior to receiving the notification email. Only the MSK study coordinator(s), PI, and ACS fellow will be given access to REDCap.

Data will be housed in the Memorial Sloan Kettering Cancer Center's (MSKCC) Jersey data center. REDCap has been approved by MSKCC's Information Security to store PHI. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections to ensure data is protected. The server is backed up nightly in the event that disaster recovery would be necessary and system would need to be rolled back. Members of the Clinical Research Administration supporting the REDCap software will have access to REDCap projects for the purpose to ensuring the proper functioning of the database and the overall software system.

Permissions to the database for both internal and external users will be managed by the REDCap project manager or study staff. User access to the data is contingent on those a part of the study team and data sharing agreements in place with third party entities if applicable. Project managers are responsible for regularly auditing these permissions to ensure changes in staff are reflected appropriately.

REDCap has the ability maintain an audit trail of changes to the database providing a timestamp as well as the user making the update. In addition, a data resolution module offers the ability of opening and closing queries optionally requiring justification when data is being updated. Permission roles for data resolution are integrated in REDCap. Comprehensive system logs are also maintained of user activity and when changes to the database are made.

After the patient's surgery, the antibiotic drug used will be documented in the study tracker. This is to track cases in which the wrong randomized drug was given to the patient.

16.1 Quality Assurance

Trained data abstractors, called Surgical Clinical Reviewers (SCRs), at each hospital collect patient information pertaining to demographics, operative details, and postoperative outcomes from the clinical record using standardized definitions up to 30 days from the index operations. Outcomes are determined directly from the medical record, by communicating with any involved providers, or from the patient directly via mail or telephone. Operations are recorded using Common Procedural Terminology (CPT®) codes. While outpatient operations are included, minor operations in free-standing surgery centers or in offices are not. Submitted data are periodically audited to ensure quality and reliability between abstractors.[12] All patient information submitted to the ACS NSQIP for quality improvement are de-identified and compliant with the Health Information Portability and Accountability Act (HIPAA) of 1996.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:
https://cancercenters.cancer.gov/documents/DSMPReviewCriteria508.pdf. The DSM

Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

Additionally, quarterly teleconferences for participating hospitals will be arranged for the duration of the trial. Investigators participating in this study will be in attendance to

discuss issues related to patient safety and trial conduction. Because this study is dependent on the ACS NSQIP mechanism, Surgical Clinical Reviewers (data abstractors) will also be in attendance at these teleconferences to ensure that all variable definitions and data collected ensure patient safety and the integrity of the study.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The study will protect the rights of all human subjects, and an informed consent will clearly define the risks, benefits, toxicities and side effects of treatment. The patients will also be informed of the alternative options for treatment. In this study, the alternative would be to proceed with national guidelines on choice of surgical antibiotic prophylaxis.

Patient data will be managed by the ACS NSQIP. The ACS NSQIP is a HIPAA-compliant registry whose data is managed by Outcome Sciences LLC, a IQVIA company. All patient data are identifiable at each hospital. However, data submitted to the ACS NSQIP for quality improvement purposes, and for the purposes of this study, are de-identified. The data privacy and security policies can be found in Appendix B.
Inclusion of Women and Minorities: Memorial Sloan Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in Section 6.0.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Lactating and pregnant women are also excluded because pancreatoduodenectomy is rarely performed for conditions that require management during lactation or pregnancy. The only clinical scenario would be a traumatic injury requiring pancreatoduodenectomy. This scenario is excluded from this study because it is not elective.

Benefits: It is possible that treatment with piperacillin-tazobactam will result in better prevention of postoperative surgical site infection as compared to cefoxitin. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will actually decrease the incidence of postoperative surgical site infections of patients undergoing pancreatoduodenectomy.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: All patients undergoing surgical procedures involving the gastrointestinal tract will receive some form of surgical antibiotic prophylaxis following national guidelines. Currently, the guideline recommends cefoxitin, used in the control arm of this study. The only alternative, therefore, is to receive the antibiotic based on national guidelines, which in this study, is the control arm.

Confidentiality: Every effort will be made to maintain patient confidentiality. Indeed, patients abstracted into the ACS NSQIP registry are de-identified, and measures are already in place at each participating institution and at the American College of Surgeons headquarters in Chicago, IL to maintain and preserve patient privacy. Data collected by the ACS NSQIP are compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Research and hospital records are confidential. Patient names or any other personally identifying information will not be used in reports or publications resulting from this study.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

Patient data will be managed by the ACS NSQIP. The ACS NSQIP is a HIPAA-compliant registry whose data is managed by Outcome Sciences LLC, a IQVIA company. All patient data are identifiable at each hospital. However, data submitted to the ACS NSQIP for quality improvement purposes, and for the purposes of this study, are de-identified. The data privacy and security policies can be found in Appendix B.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

PD is a major operation that is associated with a 1.6% mortality and a 30-40% morbidity in ACS NSQIP-HPB Collaborative institutions. Mortality and morbidity related to PD will not be considered an SAE. Hospital admission for a planned procedure/disease treatment is not considered an SAE. If a participant does not undergo a successful pancreatoduodenectomy

(PD) but received study drug will be followed for 48 hours after the procedure considering the clinical pharmacology and half-life of study drugs for participants with normal renal function.

Only grade 4-5 SAEs that are related (possible, probable, definite) to the antibiotic must be reported.
SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.
The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.2.1 SAE Reporting for the Participating Sites is described in Appendix D Multicenter Therapeutic Protocol Addendum.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A1: ACS NSQIP Standard Data Definitions

Appendix A2: ACS NSQIP Pancreatectomy Data Definitions

Appendix A3: Additional Data To Be Collected by the ACS NSQIP for this study

Appendix B: Data Privacy and Security Policy

Appendix C: Package Insert for piperacillin-tazobactam (Zosyn®)

Appendix D: Multicenter Therapeutic Protocol Addendum