The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

IV Ibuprofen for the Prevention of Post-ERCP Pancreatitis in Pediatric Patients: A Pilot Study

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1. Introduction and Purpose:

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopic technique utilized to diagnose and treat a variety of pathology in the bile ducts and pancreas [1]. Post-ERCP pancreatitis (PEP) is the most common complication following ERCP occurring in approximately 11% of children undergoing the procedure [2]. By definition it leads to prolongation of hospital stay or delays in care and rarely can result in long-term morbidity or even death [3]. Recent adult trials have demonstrated prevention of PEP with administration of rectal nonsteroidal anti-inflammatory drugs (NSAIDS) [4]. To date, no studies have been performed in children thus no “gold standard” or even commonly accepted method of preventing PEP in the pediatric population exist. Studying an IV NSAID such as ibuprofen has distinct advantages over rectally administered NSAIDs in the pediatric population. It would allow for more consistent weight based dosing and provide more predictable absorption compared to suppository. Thus, this project proposes a pilot study evaluating the effectiveness and safety of IV ibuprofen at preventing PEP in the pediatric population. The hypothesis is that single dose IV ibuprofen at the time of ERCP will decrease the incidence of PEP after the procedure. The primary endpoint will be development of PEP which will be defined utilizing consensus criteria [5]. The secondary safety endpoint will be development of gastrointestinal bleeding which will also be defined utilizing consensus criteria [5]. The goal of the study is to gather preliminary data to allow sample size calculations for a future multi-center trial and evaluate the safety of administering IV Ibuprofen at the time of ERCP. While IV ibuprofen is not currently FDA approved for use in children, it has been shown to be safely and effectively used in pediatric patients across a large spectrum of ages and weights [6-8]. Thus, it is felt that the minimal risks that may be associated with its administration justify exploring the potential benefit associated with decreasing rates of PEP in the pediatric population.

2. Background:

Clinically significant pancreatitis is the most common complication following ERCP and leads to significant morbidity and rarely death [9]. Large prospective studies involving ERCPs performed in adult patients suggest that rates of PEP can be expected to be between 1-7% for most indications, although some series have reported much higher rates of PEP when ERCP is performed for high risk indications [10]. Most of these studies utilize the “Cotton Criteria” for defining episodes of PEP: typical pain and elevated pancreatic enzymes resulting in hospitalization or delays in care of at least 2 days [11]. To gauge the true impact of this entity on patients and the health care system, it would be more appropriate to utilize more inclusive criteria such as those proposed by the American Society of Gastrointestinal Endoscopists (ASGE): typical pain and elevated pancreatic enzymes resulting in any unexpected hospitalization or delay in clinical care [5]. When such criteria are utilized, it is likely that rates of PEP are slightly higher than that commonly reported in the literature. Rates of PEP in children remain poorly defined but are thought to occur at rates similar to adult populations [12-16], Our group recently reviewed data of 436 patients followed at Children’s Medical Center (CMC) Dallas who underwent ERCP between 2004-2013 and found that PEP occurred in 11% of patients [2]. Of the patients who developed PEP, 28% of them had a moderate to severe course, highlighting the importance of addressing this adverse event in this patient population.

Currently, there is no standard of care for the prevention of PEP in the pediatric population and adopting adult based standards is problematic. Currently, pancreatic duct stenting is the most vigorously studied preventative measure in the adult literature and is considered by most endoscopist performing ERCP on adults to be the gold standard at

preventing PEP. Pancreatic duct stenting is thought to prevent PEP by overcoming edema and inadequate drainage that may result following trauma associated with the papilla manipulation that occurs during ERCP. Several meta-analyses in adults have demonstrated that pancreatic stenting is effective at reducing rates of PEP [17, 18]. In the pediatric population large studies are lacking, but the only current pediatric specific study in the literature looking at PEP suggested that pancreatic stenting did not protect patients from PEP and actually increased the likelihood of developing PEP in patients with chronic pancreatitis [19]. In our review of patients treated at CMC Dallas, we found that pancreatic stenting significantly increased rates of PEP providing further evidence that it may actually be detrimental in the pediatric population [2]. This may not be surprising, as stenting has previously been suggested to be detrimental in certain adult patient populations as well, such as patients with smaller pancreatic ducts or more viscous pancreatic secretions at baseline [20]. Even in the adult literature, research continues to try and identify alternative measures at preventing PEP, mainly because placing such stents can be technically difficult and may necessitate additional procedures to remove them. While multiple pharmacological agents have been evaluated, none has been shown to unequivocally prevent PEP [3]. Recently, there has been gathering evidence that administration of rectal NSAIDS at the time of procedure does decrease the risk of PEP [21]. The mechanism of action appears to be inhibition of mediators of the inflammatory process (prostaglandins, phospholipase A2, and neutrophil/endothelial interactions) incited during ERCP as elucidated through in-vitro studies [22], animal studies [23], as well as in-vivo studies of non-ERCP pancreatitis [24]. While studies evaluating oral NSAID at time of ERCP have not consistently shown to be beneficial at preventing PEP, rectally administered NSAIDS have been shown to be consistently effective [25]. The most recent meta-analysis looking at the effectiveness of rectal NSAIDS (indomethacin or diclofenac) included 7 randomized control trials and 2133 patients showed that rectal NSAIDs decreased the incidence of PEP (RR 0.44; 95% CI 0.34-0.57, P<0.01) with a number needed to treat of 11 [21]. While these results are extremely encouraging, there are several considerations that limit their general applicability to the pediatric population. In addition, the fact remains that no single agent has specifically been studied to prevent PEP in the pediatric population.

This study proposes a pilot study evaluating the ability of IV ibuprofen for the prevention of PEP in the pediatric population. While a rectal suppository provides a convenient relatively cheap form of drug administration in the adult population, it does not allow for the weight based dosing needed across the pediatric population. An IV formulation could overcome this limitations and allow for very predictable absorption [26]. While not currently FDA approved for use in patients <18 years of age, IV ibuprofen has been studied in a variety of pediatric conditions and found to be safe and effective. A large meta-analysis found IV ibuprofen to be as effective as indomethacin for the closure of a patent ductus arteriosus (PDA) in premature neonates with less side effects. The traditional dosing regimen for PDA closure is 10mg/kg followed by 5mg/kg at 24hr and 48hrs (10-5-5 mg/kg). More recently, a higher dose regimen (20-10-10 mg/kg) was found to be more effective at achieving PDA closure without increasing risk of side-effects [27]. IV ibuprofen has also been studied in older children and adolescents in the setting of post-tonsillectomy pain. A recent multicenter study of single dose IV ibuprofen at 10mg/kg given just prior to tonsillectomy, a procedure associated with a relatively high risk of bleeding, showed no increased risk of bleeding [8]. In a meta-analysis of all NSAIDS given during tonsillectomy which evaluated 1101 children in 15 studies (not including the above study) a non-significant increase in the risk of bleeding requiring surgical intervention (OR 1.69, 95% CI 0.71-4.01) was seen. There was no increased risk of bleeding that required non-surgical intervention (OR 0.99, 95% CI 0.41-2.40). When ketorolac was excluded from the analysis, the risk of bleeding requiring

surgical intervention decreased (OR 0.89, 95% CI 0.28-2.83) and bleeding requiring non-surgical intervention decreased as well (OR 0.30, 95% 0.04-3.46). To date there has been no study suggesting that there is a trend towards increased bleeding rates when IV ibuprofen is utilized during tonsillectomy. This is an important consideration, as 1-2% of patients undergoing ERCP may experience clinically significant bleeding as a result of the procedure [9].

The proposed study is unique as it is the first to evaluate an IV NSAID for the prevention of PEP and it is the first to evaluate any pharmacologic intervention to prevent PEP in the pediatric population. In addition, previous studies have focused mainly on patient populations identified to be at "high risk" for developing PEP. This is possible because risk factors for the development of PEP have been well identified in the adult population [28]. This is problematic as even low risk adult patients can develop moderate to severe PEP, and a high-risk pediatric population has not been appropriately identified. We would argue that a PEP incidence of 11% justifies administration of a preventative intervention in all pediatric patients undergoing the procedure, particularly if the intervention can be shown to be safe and effective. Thus, this study proposes a randomized control trial to study single dose IV ibuprofen at a dose of 10mg/kg (max 800mg) at the time of ERCP for the prevention of PEP in pediatric patients undergoing ERCP.

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3. Concise Summary of Project:

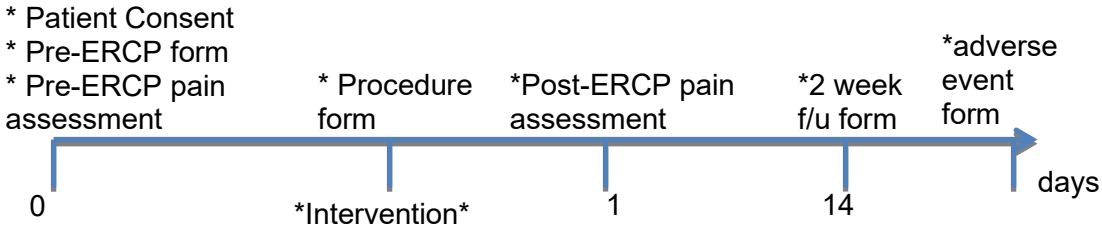
This project proposes a pilot study evaluating the effectiveness of IV ibuprofen at preventing PEP in the pediatric population. The goal of the study is to gather preliminary data to allow sample size calculations for a future multi-center trial and evaluate the safety of administering IV Ibuprofen at the time of ERCP. The design of the proposed study is a prospective randomized double-blind control trial comparing IV Ibuprofen to placebo (normal saline) at the time of procedure in all patients undergoing ERCP at Children's Medical Center over a two year period. IV ibuprofen will be given as a single dose of 10mg/kg (max: 800mg) at the time of endoscopy. It will be drawn up from a single use vial and diluted with normal saline to a concentration of 4mg/ml and will be infused over a 15 minute time period. Those assigned to receive the placebo control will receive an equivalent amount of normal saline only over the same time period. 128 eligible patients are expected to be encountered over the two-year study period. A total of 120 patients will be consented for this study (60 to receive placebo, 60 to receive IV ibuprofen). The main outcome measurement will be development of PEP. Rates of post-ERCP bleeding will also be measured as a secondary safety endpoint. The results of this study will be utilized for the developing a larger multicenter study.

4. Study Procedures:

This study is designed as a prospective, randomized, double-blinded, clinical trial. We plan to enroll 120 consecutive patients undergoing ERCP at CMC Dallas over a two year study

period. All patients will be enrolled at CMC Dallas by study team members. Figure 1 displays approximate timing of all study procedures.

Figure 1: Study Procedures



After a decision is made that a patient will undergo ERCP and before the procedure is performed, a member of the study team will approach the patient and their family for participation and consent. All providers who perform ERCP at CMC Dallas are members of the study team, which should allow for efficient screening of all potential subjects. After consent is obtained, a study team member will fill out the pre-procedural form to collect demographic information as well as clinical information to quantify anticipated disposition and risk for developing AEs (Appendix A). All study patients will also undergo a pre-procedural pain assessment. Communicative patients will be asked to mark their level of pain on a Likert scale. Non-communicative patients will have the pain assessment completed by a legal guardian (Appendix E). Consenting patients will be randomly assigned to receive a single dose of either 10mg/kg (not to exceed 800mg) IV-ibuprofen or IV-normal saline at the time of scope insertion and patients will subsequently undergo ERCP as planned. The patient, study team, and endoscopist will be blinded to the intervention. Upon completion of the procedure a study team member will fill out the procedural form to document any intra-operative AEs as well as techniques performed during the procedure that may predispose to the development of AEs (Appendix B).

Subsequent management will be dictated by routine clinical care practices. Patients undergoing a planned outpatient procedure will be monitored after the procedure for at least 60 minutes per routine post-op protocol after which they may be discharged at the discretion of the care team. Decisions for unplanned admissions to manage abdominal pain, bleeding or any other adverse event will be made at the discretion of the care team. Patients who are unexpectedly admitted because of post-operative pain will have amylase and lipase drawn the morning following the procedure to determine if PEP is present per routine clinical practice. For those who experience clinical signs of bleeding, a CBC will be drawn at least once during the course of the admission after gastrointestinal bleeding is identified (hematemesis, hematochesia, or melena) to evaluate for development of post-ERCP bleeding. Subsequent lab draws and clinical management will be at the discretion of the clinical service caring for the patient. The patient will be followed until management of the adverse event is complete after which a study team member will fill out an adverse event form (Appendix C).

Patients undergoing an inpatient procedure, or who will have a planned admission after ERCP will have amylase/lipase drawn the following day if abdominal pain concerning for pancreatitis develops that is likely to lead to delayed discharge or further delays in clinical care, which would constitute routine clinical care. Similarly, a CBC will be drawn on any inpatient who demonstrates clinical evidence of gastrointestinal bleeding (hematemesis, hematochezia, or melena). Subsequent lab draws and clinical management will be at the discretion of the clinical service caring for the patient. The patient will be followed until

management of the adverse event is complete after which a study team member will fill out an adverse event form (Appendix C).

All enrolled patients will undergo a post-operative pain assessment which will be conducted by a member of the study team 24 hours (defined as between 20-28 hours) after the ERCP. For current inpatients, the patient or a legal guardian will be asked to describe their level of pain on a Likert scale in a fashion analogous to the pre-procedural assessment. They will have a copy of their pre-procedural pain assessment for reference. For discharged patients, a phone assessment will be made where they will be asked to rate their pain on a scale of 1-10. They will have been given a copy of their pre-procedural pain assessment for reference. The post-procedure pain score will be recorded by a study team member (Appendix E). An amylase and lipase will be drain on all patients who have a pain score which increases between the pre-operative and post-operative evaluation as would be a part of routine clinical care. This information will be made available to both study team members and the primary care team for the patient to aid with clinical decision making.

Two weeks after the procedure, a follow-up phone call or clinic visit will occur as is routine clinical practice for all patients undergoing ERCP at CMC Dallas. The information gathered from this two week follow-up communication will be filled out into the 2-week f/u form (Appendix D). The purpose of this interaction will be to identify patients who experienced an adverse event that might otherwise have been missed. For those patients in whom an AE is identified during this interaction, the AE will be followed to completion and then the adverse event form will be filled out by a study team member. For those patients who are unable to be reached at the two-week time point, three additional attempts will be made to reach the participant by phone. If after these attempts no contact is made, this will be noted on the follow-up form and the information available in the medical record will be utilized to determine if an AE occurred. This communication will not occur before 14 days following the procedure and all additional attempts to reach the family will be completed by 30 days following the procedure.

The subject will not be responsible for any research-related costs and will not be compensated for participating. Patient's participation will be completed upon completion of the two week follow-up interaction or upon completion of the management of any AEs, whichever is longer. For study purposes, no patient is anticipated to be followed for more than two months time. For patient's whom require ongoing management of their AEs beyond two months time will have their AEs characterized according to the information available up until that time point utilizing the standardized criteria previously mentioned.

Defining AEs:
This study will monitor for both procedure related AEs as well as potential drug related AEs. Procedure related AEs will be systematically characterized utilizing the American Society of Gastrointestinal Endoscopy (ASGE) lexicon for AEs. Accordingly, a procedure relate AE will be defined as any event that prevents completion of the planned procedure and/or results in admission to hospital, prolongation of existing hospital stay, another procedure, or subsequent medical consultation. A listing of all procedure related AEs that will be specifically monitored for during this study, along with their associated definition can be found in Table 1 below.

Procedural Related AEs	**Definition**
Pancreatitis	Typical pain, amylase/lipase>3xULN

(primary endpoint)	
Bleeding (secondary endpoint)	Hematemesis and/or melena or hemoglobin drop>2grams
Pain	New or increased abdominal pain not related to pancreatitis or other AE.
Cholangitis	Fever >38C, >24 hours after procedure AND new or worsening cholestasis
Fever without a source	Fever >38C, >24 hours after procedure AND without an obvious source
Perforation	Evidence of air or luminal contents outside the GI tract
Other (specify)	Other procedure related adverse event not captured by definitions listed above

Each procedure related AE will be characterized in terms of timing (pre-procedural, intraprocedural, <14 days post procedural, or >=14 days post procedural), likelihood of attribution (definite, probable, possible, unlikely) and severity (see Table 2 below). While all procedural related AEs will be recorded, only probable or definite cases of PEP or post-ERCP related bleeding will be included in the final analysis of the primary and secondary endpoints.

Consequence	**Mild**	**Moderate**	**Severe**	**Fatal**
Procedure aborted because of AE	X			
Post-procedure medical consultation	X			
Unplanned anesthesia support		X		
Unplanned admission or prolongation of hospital stay for <=3 nights	X			
Unplanned admission or prolongation for 4-10 nights		X		
Unplanned admission or prolongation for >10 nights			X	
ICU admission for 1 night		X		
ICU admission for >1 night			X	
Transfusion		X		
Repeat endoscopy for AE		X		
Interventional radiology for AE		X		
Interventional treatment for integument injuries		X		
Surgery for AE			X	
Permanent disability (specify)			X	
Death				X

Table 2: Severity grading for AEs.

Drug related AEs will be monitored throughout the study until the 2 week follow-up interaction is completed. They will be defined as any untoward or unfavorable medical occurrence including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research and will be elicited through direct patient interaction at 24 hours and 2 weeks after the procedure as well as review of the

medical record up to 2 weeks following the procedure. Table 3 shows the definitions that will be utilized to define potential drug related AEs. The ASGE lexicon definitions outlined above will be utilized to categorize these AEs in terms of timing, attribution, and severity.

Drug Related AE	Definition
Infection	Any infection (ex: bacteremia, pneumonia, cholangitis) which is documented or presumptively treated during the course of study involvement.
Bronchospasm	Any new or increased use of any bronchodilator during the course of study involvement.
Hypoxia	Any new or increased oxygen requirement during the course of study involvement.
Hematemesis	Any visible blood in emesis during the course of study involvement.
Hematochesia	Any visible blood in stool during the course of study involvement.
Skin reaction	Any new rash during the course of study involvement.
Elevated creatinine	Creatinine increase above baseline and elevated for age during the course of study involvement.
Allergic Reaction	Any clinical condition felt to be a reaction to a medication or product as determined by their provider during the course of study involvement.
Cardiovascular thrombotic event	Any documented myocardial infarction or stroke during the course of study involvement.
Other (specify)	Any untoward or unfavorable medical occurrence including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research not captured by definitions above

Table 3: Study lexicon for potential drug related AEs which will be specifically monitored for in this study

5. Sub-Study Procedures:
Not applicable

6. Criteria for Inclusion of Subjects:
Age<=18 years
Undergoing ERCP (defined as cannulation of the major or minor papilla) for any indication

7. Criteria for Exclusion of Subjects:
Age>18
Pancreatitis within the 72 hours preceding ERCP
Allergy or hypersensitivity to Aspirin or NSAID medications
Pregnancy or breastfeeding mother

Cr >1.4
Gastrointestinal hemorrhage in preceding 72 hours
Heart disease reliant upon a patient ductus arteriosis
History of sickle cell disease

8. Sources of Research Material:
The laboratory data that will be collected and utilized during this study is data that will be generated as part of routine clinical care. No data will be specifically collected for research purposes only. All data will be obtained from the medical records at CMC Dallas.

9. Recruitment Methods and Consenting Process:
All potential subjects will be patients of the investigators as they perform all ERCPs at CMC Dallas. Potential subjects will be approached for inclusion after the decision is made that an ERCP will be performed and before the procedure is performed. Patient of all ages and ethnicities will be approached for consent. For those patients between the age of 12 and 18, parental consent and patient assent will be obtained. For Spanish speaking patients, a short form Spanish consent will be obtained after the study is fully explained to them in their native language. Every effort will be made to minimize the potential for undue influence or coercion. It will be emphasized that patients will receive the same care whether they participate in the study or not. In addition the potential benefits of participating in the study will not be overly exaggerated.

10. Potential Risks:
Since its introduction as a possible PEP preventative measure, the fear is that NSAIDS may increase risks of bleeding associated with ERCP. Multiple studies suggest that the standard risk of clinically significant bleeding after ERCP is in the range of 1-2% [9]. While IV ibuprofen has not been studied in the setting of ERCP, there is now a fair amount of surgical literature to suggest that NSAIDS, and ibuprofen in particular, do not increase risks of bleeding in general. A recent meta-analysis of NSAIDs (indomethacin and diclofinac) during ERCP showed no increased risk of clinically significant bleeding compared to placebo [21]. A recent multicenter study of single dose IV ibuprofen at 10mg/kg given just prior to tonsillectomy, another procedure associated with a relatively high risk of bleeding, showed no increased risk of bleeding [8]. In a meta-analysis of NSAIDS given during tonsillectomy which evaluated 1101 children in 15 studies, a non-significant increase in the risk of bleeding requiring surgical intervention (OR 1.69, 95% CI 0.71-4.01) was seen. There was no increased risk of bleeding that required non-surgical intervention (OR 0.99, 95% CI 0.41-2.40). When ketorolac was excluded from the analysis, the risk of bleeding requiring surgical intervention decreased (OR 0.89, 95% CI 0.28-2.83) and bleeding requiring non-surgical intervention decreased as well (OR 0.30, 95% 0.04-3.46) [7].To date there has been no study suggesting that there is a trend towards increased bleeding rates when IV ibuprofen is utilized during tonsillectomy. Thus, based on the available literature, we feel that there is unlikely to be increased risk of bleeding with a single dose of IV ibuprofen given at the time of ERCP. That being said, because this procedure is associated with a relatively high rate of bleeding complications and IV ibuprofen has not been specifically evaluated for this indication, it is a secondary outcome that will be monitored.

In this study we will be utilizing placebo (normal saline) controls. In the adult population, placing a pancreatic stent has been shown to reduce rates of PEP and is considered by many to be “the gold standard” [17, 18]. Pancreatic stenting to prevent PEP has not been specifically evaluated in the pediatric population. In reviewing our data at CMC Dallas since 2004, we found that placing a pancreatic stent in patients who had their pancreatic duct

injected during ERCP (a population we found to be at high risk for PEP on a multivariate analysis), rates of PEP actually increased significantly (20% vs 34%, p-value 0.041) [2]. Indeed, it has been suggested that certain adult populations (smaller pancreatic ducts, thicker secretions) may not benefit from pancreatic stent placement and that they may actually be detrimental [20]. Combining the fact that placing a pancreatic stent is technically difficult with the paucity of data behind pancreatic stenting to prevent PEP in children has lead many endoscopists performing endoscopy in children to abandon the practice. Taking this into account, along with our personal experience with stenting outlined above, we conclude that it is both ethical and appropriate to utilize placebo as opposed to pancreatic stenting for our control patients.

11. Subject Safety and Data Monitoring:
Currently, IV ibuprofen is not FDA approved for the prevention of post-ERCP pancreatitis or in patients <18 years of age. Thus, this study will be filing an Investigational New Drug (IND) application with the FDA and await approval prior to enrollment. This study team will also adhere to the following Data Safety Monitoring Plan (DSMP).

A blinded interim analysis by an independent reviewer (Dr. Lillienne Chan, a pediatric gastroenterologist at UT Southwestern Medical Center who is familiar with clinical research design and analysis) will be performed after 60 patients are enrolled (50% of the total study enrollment) or sooner if one of the following criteria are met:

- 12 episodes of post-ERCP pancreatitis occur or
- 3 episodes of post-ERCP bleeding occur

These numbers were chosen because this would represent a doubling of the expected rate of post-ERCP pancreatitis and post-ERCP bleeding to be experienced in 60 patients.

For each subject, the reviewer will be provided with the following:

- Study identification number
- Whether or not the primary endpoint occurred (PEP)
- Whether or not the secondary endpoint occurred (post-ERCP bleeding)
- In which group (A or B) the patient belonged

If >66% of the post-ERCP pancreatitis or post-ERCP bleeding events occur in a particular group, the independent reviewer will break the code linking which intervention the patients received (IV Ibuprofen or placebo). This value was selected because it represents a 2:1 (double) frequency of the endpoint outcomes. The study will be stopped if either endpoint occurs at this high rate in the IV Ibuprofen group. If the increased rate of pancreatitis is seen in the control group, then a formal statistical analysis will be performed and statistical significance will only be declared if the two-sided p value is less than 0.05 at which point the study will be terminated as it would be unethical to withhold IV Ibuprofen from future patients. If the independent reviewer is required to break the code, the study team members will not be aware of this fact unless the study must be terminated. The study team will only be told if they may continue the study or not.

12. Procedures to Maintain Confidentiality:
Patient, demographics, pre-procedural and procedural based risk factors, and follow-up data (Appendix A-D) will be entered into a REDCaps database in a de-identified fashion providing an encrypted mode of data storage that minimizes the risk of loss of confidentiality. Only study team members will be provided access to the REDCaps database. A separate password protected excel file linking patients MRN to their study identification number will be

maintained by the primary investigator. This file will be located on the secure departmental drive only. No information will be disclosed to outside persons or entities.

13. Potential Benefits:
Research subjects who are randomized to the IV ibuprofen group may experience decrease rates of PEP (study primary outcome). Overall, this study is designed to identify a potential therapeutic means of preventing PEP in all pediatric patients who undergo ERCP. The data from this study will be utilized in the design of a larger multicenter clinical trial. It is the first study of its kind, designed to specifically evaluate the ability of a pharmacologic agent to prevent PEP in pediatric patients.

14. Biostatistics:
In 2013, 59 ERCPs were performed at CMC Dallas, 56 of whom would have met inclusion/exclusion criteria for this study. As we experience an approximate 10% increase in ERCP volume annually, it is reasonable to estimate that we will encounter 128 patients who will meet inclusion criteria over the two-year study period.

The PEP incidence rate in the control group is estimated to be 11% based on CMC historical data. A recent meta-analysis suggests that NSAIDS at the time, or just after ERCP reduces the incidence of PEP by 51% [25]. Assuming a 50% reduction can be achieved with IV Ibuprofen, the incidence rate in the treatment group is estimated to be 5% over the same time period. With a sample size of 120 (60 in the treatment group and 60 in the control group), the power to detect a significant difference is 22.1%. Although it is underpowered, this pilot study will provide valuable information toward the design of a larger multicenter randomized clinical trial.

The primary endpoint analysis will utilize the Fisher's exact test or chi square test (depending on sample size) to analyze the difference in the proportion of patients with post-ERCP pancreatitis in the indomethacin group and the placebo group. A difference will be considered significant at p-value <0.05 (two-sided). Similarly, the secondary endpoint analysis will utilize the Fisher's exact test or chi square test (depending on sample size) to analyze the difference in the proportion of patients with post-ERCP bleeding in the indomethacin group and the placebo group. A difference will be considered significant at p-value <0.05 (two-sided). The incidence and severity of all adverse events throughout the study duration will be summarized using descriptive statistics.