Stent vs. Indomethacin for Preventing Post-ERCP Pancreatitis: The SVI Trial

A Multicenter Randomized Non-Inferiority Clinical Trial of Rectal Indomethacin Alone

vs.

Indomethacin & Prophylactic Pancreatic Stent Placement for Preventing Post-ERCP Pancreatitis in High-Risk Cases

NCT02476279

STUDY GROUP CHAIR
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Original Protocol: September 7, 2015
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Investigators' Agreement

I have read the attached clinical protocol titled "Stent vs. Indomethacin for Preventing Post-ERCP Pancreatitis: The SVI Trial" revised in February 15, 2021 and agree to conduct the protocol as written in this document.

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

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

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

_____ _____

Signature of Principal Investigator Date

_____

Printed name of Principal Investigator

_____ _____

Signature of Co-Principal Investigator (When applicable) Date

_____

Printed name of Co-Principal Investigator (When applicable)

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1.0 SUMMARY

Protocol Title	Stent vs. Indomethacin for Preventing Post-ERCP Pancreatitis
Acronym	SVI
Clinical Trial Phase	Phase III
Study Sites	Approximately 20 clinical centers in the United States and Canada
Study Period	Planned enrollment period – 7.5 years Planned duration of the study – 8 years
Study Population	Patients undergoing high-risk ERCP who require pancreatic stent placement for the sole purpose of pancreatitis prevention.
Primary Study Objective	To assess whether rectal indomethacin alone is non-inferior to the combination of rectal indomethacin and prophylactic pancreatic stent placement (PSP) for preventing post-ERCP pancreatitis (PEP) in high-risk cases.
Secondary Study Objective	To establish a repository of whole blood, serum, plasma, urine, duodenal fluid, and stool from study subjects that will allow future translational research elucidating the molecular and genetic mechanisms of PEP, as well as the mechanisms by which non-steroidal anti-inflammatory drugs prevent this complication.
Study Design	A comparative effectiveness, multi-center, randomized, double blind, non-inferiority study of rectal indomethacin alone vs. the combination of rectal indomethacin and prophylactic pancreatic stent placement for the prevention of post-ERCP pancreatitis in high-risk cases.
Sample Size	A maximum sample size of 2180 subjects (1090 in each arm) will be needed for 85% power to rule out that the upper two-sided 95% confidence limit for the absolute difference between the two groups is greater than 5% in favor of combination therapy.
Inclusion Criteria	Any patient undergoing ERCP in whom pancreatic stent placement is planned for post-ERCP pancreatitis prevention, is ≥ 18 years old, who provides informed consent, AND: Has **one** of the following: 1. Clinical suspicion of or known sphincter of Oddi dysfunction 2. History of post-ERCP pancreatitis (at least one prior episode of pancreatitis after ERCP)

	3. Pancreatic sphincterotomy 4. Pre-cut (access) sphincterotomy (including septotomy) 5. Difficult cannulation: cannulation duration ≥ 6 minutes (starting at time of initial papillary engagement with at least 25% of the time in contact with the papilla) AND/OR ≥ 6 cannulation attempts (defined as sustained contact with papilla lasting at least 1 second). 6. Short-duration (≤ 1 min) balloon dilation of an intact biliary sphincter. Or has **at least 2** of the following: 7. Age < 50 years old **&** female gender 8. History of recurrent pancreatitis (at least 2 episodes) 9. ≥3 pancreatic injections 10. Pancreatic acinarization 11. Pancreatic brush cytology
Exclusion Criteria	1. Ampullectomy 2. Cases in which a pancreatic stent must be placed for therapeutic intent 3. Unwillingness or inability to consent for the study 4. Pregnancy 5. Breast feeding mother 6. Standard contraindication to ERCP 7. Allergy to Aspirin or NSAIDs 8. Ongoing or recent (within 1 week) hospitalization for acute pancreatitis, or known ongoing biochemical or anatomic evidence of unresolved pancreatic injury. 9. Known chronic calcific pancreatitis 10. Suspected pancreatic head malignancy 11. Procedure performed on major papilla/ventral pancreatic duct in patient with pancreas divisum (no manipulation of minor papilla) 12. ERCP for biliary stent removal or exchange without anticipated pancreatogram 13. Subjects with prior biliary sphincterotomy now scheduled for repeat biliary therapy without anticipated pancreatogram 14. Anticipated inability to follow protocol 15. Absence of rectum
Study Intervention and Follow-up	Subjects will undergo ERCP per clinical indication. During the procedure, if the attending endoscopist determines that

	inclusion criteria have been met and none of the exclusion criteria are present, the subject will be randomized to receive a 100 mg of rectal indomethacin (two 50 mg suppositories) only or the combination of prophylactic stent and 100 mg of rectal indomethacin. Subjects will be contacted at 5 and 30 days after the ERCP to assess for the development of outcome events.
Primary Outcome Measure	The primary endpoint is post-ERCP pancreatitis, defined per consensus (Atlanta) criteria: 1) New or increased pain in the upper abdomen **and** 2) amylase or lipase ≥ 3x the upper limit of normal 24 hours after the procedure **and** 3) hospitalization (or prolongation of existing hospitalization) for at least 2 days (at least night of ERCP & next night). This outcome will be adjudicated by a blinded panel.
Statistical Analysis for Primary Outcome Measure	An intention-to-treat approach will be the primary basis for analysis of the primary outcome measure. The two-sided 95% upper confidence bound of the risk difference in the observed proportion of patients developing post-ERCP pancreatitis between the two treatment groups will be calculated.

1.1 Acronyms

DSMB Data and Safety Monitoring Board

DSMP Data and Safety Monitoring Plan

ERCP Endoscopic Retrograde Cholangiopancreatography

FDA Food and Drug Administration

GCP Good Clinical Practice

ICH International Conference on Harmonisation

IRB Institutional Review Board

MoP – Manual of Procedures

MSM Medical Safety Monitor

MUSC Medical University of South Carolina

NCI National Cancer Institute

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Institutes of Health

NSAIDs Non-Steroidal Anti-Inflammatory Drugs

OPRR Office for Protection from Research Risks

PEP Post-ERCP Pancreatitis

PI Principal Investigator

PSP Pancreatic Stent Placement

RCT Randomized Controlled Trial

REB Research Ethics Board

SAE Severe Adverse Event

SC Steering Committee

SDMC Statistical & Data Management Center

SOD Sphincter of Oddi Dysfunction

SSL Secure Socket Layer

SVI Stent vs. Indomethacin

UM University of Michigan

2.0 OBJECTIVES

2.1 Primary

To assess whether rectal indomethacin alone is non-inferior by a pre-specified amount therapeutic effect to the combination of rectal indomethacin and prophylactic pancreatic stent placement (PSP) for preventing post-ERCP pancreatitis (PEP) in high-risk cases.

2.2 Secondary

1. To assess whether rectal indomethacin alone is non-inferior by a pre-specified amount **therapeutic effect** to the combination of rectal indomethacin and PSP for decreasing the severity of PEP in high-risk cases.
2. To establish a repository of whole blood, serum, plasma, urine, duodenal fluid, and stool from study subjects that will allow future translational research elucidating the molecular and genetic mechanisms of PEP, as well as the mechanisms by which non-steroidal anti-inflammatory drugs prevent this complication.

3.0 BACKGROUND AND RATIONALE

3.1 Background

Post-ERCP Pancreatitis remains a significant public health issue:

Pancreatitis is the most frequent complication of endoscopic retrograde cholangiopancreatography (ERCP) occurring in 2-10% of cases[1] and accounting for substantial morbidity, occasional mortality, and increased health care expenditures. Twelve percent of those who develop post-ERCP pancreatitis (PEP) will follow a severe clinical course that results in prolonged hospitalization or additional interventions, leading to significant patient suffering.[2] It has been estimated that over 700,000 ERCP procedures are performed in the United States annually. Assuming a mid-range post-ERCP pancreatitis rate of 5%, over 35,000 cases of PEP occur in the US each year. Average Medicare reimbursement for PEP is approximately $6000, resulting in an estimated annual cost burden in excess of $200 million.

Preventing post-ERCP pancreatitis:

Until recently, only pancreatic stent placement (PSP) had been shown to be effective in preventing PEP.[3,4] PSP has become common clinical practice in the United States,[5,6] however it remains technically challenging, time consuming, and costly.[7-10] Moreover, attempting to place a pancreatic stent with subsequent failure actually increases the risk of PEP above baseline by inducing injury to the pancreas.[11,12] Additionally, studies demonstrating the efficacy of PSP were conducted at referral centers by expert endoscopists who are highly skilled in pancreatic intervention – clinical outcomes from broader practices are not available and it seems likely that the effectiveness of PSP may be lower in less expert hands – and the risks higher, potentially mitigating the benefits of this intervention.

Recently, we reported the results of our multi-center double-blind, randomized, controlled trial (RCT) demonstrating that rectal administration of indomethacin, a non-steroidal anti-inflammatory drug (NSAID), significantly reduces the incidence and severity of PEP in high-risk cases.[13] On the background of a prior meta-analysis showing that rectal NSAIDs are effective in preventing PEP,[14] as well as the 2010 European Society of Gastrointestinal Endoscopy guidelines recommending rectal NSAIDs to all patients undergoing ERCP,[15] this groundbreaking study, funded through the NIH-NIDDK R21 mechanism, has immediately, broadly, and meaningfully impacted clinical practice worldwide by convincing the GI community that rectal indomethacin has a concrete, beneficial role in ERCP practice. Several recent meta-analyses have confirmed the effectiveness of rectal NSAIDs for preventing post-ERCP pancreatitis, and existing practice guidelines recommend their use in all patients undergoing ERCP.

Rectal indomethacin could replace pancreatic stent placement for preventing PEP:

The aforementioned RCT enrolled 602 patients at elevated risk for PEP, most of whom (>80%) had undergone pancreatic stent placement. Secondary analysis revealed that those who received indomethacin and a pancreatic stent (n=247) had a PEP rate of 9.7% compared to 16.1% in subjects who received a stent alone (n=249) (p=0.04). Therefore, this trial showed that indomethacin confers protection *in addition* to PSP, however there are no studies examining whether indomethacin is effective when administered *instead* of PSP. If indomethacin were to obviate the need for pancreatic stent placement, major clinical and cost benefits in ERCP practice could be realized (see below).

To further explore this possibility, we performed a *post hoc*, hypothesis-generating analysis of our indomethacin RCT which suggested that subjects who received indomethacin alone were less likely to develop PEP than those who received a pancreatic stent alone or the combination of indomethacin and stent, even after adjusting for underlying differences in subject risk.[16] Additionally, a recent network meta-analysis comparing the data supporting PSP with those supporting prophylactic NSAIDs demonstrated that rectal NSAIDs alone are not inferior to the combination of NSAIDs and PSP for preventing PEP.[17]

Prophylactic pancreatic stent placement is thought to reduce the risk of PEP by relieving pancreatic ductal hypertension that develops due to procedure-induced edema and stenosis of the pancreatic orifice.[1,8,9] PSP, however, is not completely effective because orifice edema is only one of several relevant pathophysiologic mechanisms in PEP. Other factors, such as chemical, allergic, enzymatic, and infectious injury are also likely to contribute to PEP,[1] and may be induced or potentiated by the process of placing a pancreatic stent. Indeed, the superiority of indomethacin mono-prevention over any strategy involving PSP is biologically plausible because the indomethacin strategy avoids manipulation of the pancreatic orifice and instrumentation of the pancreatic duct.

3.2 Rationale

The SVI trial is a natural next step in the advancement of our understanding of PEP prevention by answering a critically important clinical question: ***can we replace an invasive and costly preventive intervention with a safe and inexpensive one?***

Potential impact of replacing PSP with rectal indomethacin prophylaxis:

Research focusing on whether PSP remains necessary in the era of indomethacin prophylaxis is critical because replacing prophylactic stent placement by indomethacin mono-prevention in clinical practice has the following major potential advantages:

1. Improving clinical outcomes by avoiding the phenomenon of attempted but failed PSP, which is associated with a high rate of PEP by causing pancreatic orifice injury but providing no ductal decompression.[11,12] As mentioned, PSP is generally (but not universally) successful and effective in expert hands, however there are no data evaluating the success rates and effectiveness of PSP in real-life practice – it is possible that this phenomenon of failed PSP is occurring more frequently than has been reported in clinical trials from expert research centers.
2. Improving clinical outcomes by avoiding the significant non-pancreatitis complications induced by PSP. Complications such as stent migration and duct perforation occur in up to 4% of cases.[4] Rare complications may also occur during follow-up upper endoscopy to retrieve retained stents.
3. Improving clinical outcomes because indomethacin alone may actually be more effective for preventing PEP than any strategy that employs PSP. As mentioned above, a *post hoc* analysis of our indomethacin RCT revealed that, after adjusting for underlying imbalances in the prevalence of risk factors for PEP between groups, subjects who received indomethacin alone (7.1% PEP rate) appeared to be at lower risk for PEP than subjects who received no prophylaxis (23% PEP rate), those who received PSP alone (16% PEP rate), and those who received the combination of indomethacin and PSP (9.5% PEP rate).[16] Indomethacin alone may be more effective than any strategy involving PSP because it avoids manipulation of the pancreatic orifice and instrumentation of the pancreatic duct, interventions that are necessary to place a pancreatic stent but are also known to contribute to pancreatitis.
4. Substantially reducing healthcare expenditures by eliminating the cost of stent placement in most cases, as well as eliminating the need for follow-up abdominal radiography (to ensure spontaneous passage of the stent) and follow-up upper endoscopies to remove retained stents. A cost-benefit analysis using data from our indomethacin RCT, published literature, and publicly available cost data, revealed that a prevention strategy employing rectal indomethacin alone could save approximately $150 million annually in the United States compared with a strategy of PSP alone, and $85 million compared with a strategy of indomethacin and PSP.[16]
5. Allowing broader delivery of care to more patients (particularly in resource-limited environments) by allowing additional time for other endoscopic procedures and interventions. Since PSP requires approximately 10 minutes to perform,[10] indomethacin mono-prevention would save 1 million procedural minutes (or 16,666 procedure hours) annually in the US, beneficial to patients and endoscopy units alike. For example, the time saved by not placing pancreatic stents in high-risk ERCP cases would allow unit and physician manpower to perform over 20,000 additional screening colonoscopies in the United States annually (assuming 45 minutes per colonoscopy).

4.0 STUDY PLAN

4.1 Study Design

This is a comparative effectiveness, multi-center, randomized, double blind, non-inferiority study of rectal indomethacin alone vs. the combination of rectal indomethacin and prophylactic pancreatic stent placement for the prevention of post-ERCP pancreatitis in high-risk cases.

4.2 Study Sites

The study will be conducted at approximately twenty tertiary care academic medical centers in the United States and Canada. Each study center will have a site PI who is responsible for the overall direction of the study at the site level, and a full study coordinator who will be responsible for consenting and enrolling patients, conducting follow-up, inputting data for local subjects, obtaining medical records for subjects hospitalized after ERCP, and procuring and processing bio-samples. Additionally, the Statistical & Data Management Center (SDMC) team will include a senior statistician, statistical analyst, data manager, database programmer, project manager, and clinical monitor(s). The collective goal of this research team is to ensure the on-budget, on-time execution of the study with the highest possible ethical, regulatory, and scientific integrity.

4.3 Recruitment

The SVI trial will enroll a maximum of 2180 patients over 7.5 years. Therefore, an enrollment goal of 3 patients per site per month is necessary. We believe that this enrollment requirement is achievable given the volume of high-risk ERCP with stent placement performed at each of the sites.

4.4 Estimated Study Duration and Timeline

Initiation of Study	3 months
Subject Recruitment	90 months
Pre-Treatment/Treatment/Follow-up	1 month
Site Close Out/Analysis and Reports	5 months
Total:	**96 months**

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for enrollment into the trial:

Any patient undergoing ERCP in whom pancreatic stent placement is planned for the purpose of PEP prevention, is ≥ 18 years old, who provides informed consent, AND:

Has **one** of the following:

1. Clinical suspicion of or known sphincter of Oddi dysfunction
2. History of post-ERCP pancreatitis (at least one prior episode of pancreatitis after ERCP)
3. Pancreatic sphincterotomy
4. Pre-cut (access) sphincterotomy (including septotomy)

5. Difficult cannulation: cannulation duration ≥6 minutes (starting at time of initial papillary engagement with at least 25% of the time in contact with the papilla) AND/OR ≥6 cannulation attempts (defined as sustained contact with papilla lasting at least 1 second).
6. Short-duration (≤ 1 min) balloon dilation of an intact biliary sphincter.

Or has **at least 2** of the following:

7. Age < 50 years old **&** female gender
8. History of recurrent pancreatitis (at least 2 episodes)
9. ≥3 pancreatic injections
10. Pancreatic acinarization, defined as opacification of pancreatic parenchyma with ductal contrast injection
11. Pancreatic brush cytology

5.2 Exclusion Criteria

1. Ampullectomy
2. Cases in which a pancreatic stent must be placed for therapeutic intent
3. Unwillingness or inability to consent for the study
4. Pregnancy
5. Breast feeding mother
6. Standard contraindications to ERCP
7. Allergy to Aspirin or NSAIDs
8. Ongoing or recent (within 1 week) hospitalization for acute pancreatitis, or known ongoing biochemical or anatomic evidence of unresolved pancreatic injury.
9. Known chronic calcific pancreatitis
10. Suspected pancreatic head malignancy
11. Procedure performed on major papilla/ventral pancreatic duct in patient with pancreas divisum (no manipulation of minor papilla)
12. ERCP for biliary stent removal or exchange without anticipated pancreatogram
13. Subjects with prior biliary sphincterotomy now scheduled for repeat biliary therapy without anticipated pancreatogram
14. Anticipated inability to follow protocol
15. Absence of rectum

6.0 SUBJECT RECRUITMENT

6.1 Screening of Potential Subjects

All patients presenting to participating study centers for ERCP will be screened before the procedure for the presence of pre-procedural exclusion criteria. If no pre-procedural exclusion criteria are present, the potential study subject will be interviewed by a research coordinator to evaluate for pre-procedural inclusion criteria and obtain informed consent.

Ongoing study recruitment efforts at each center will include the maintenance of a Screen Failure Log for the purpose of documenting the center population from which the subjects in this trial are

drawn who are not eligible for the study. All patients in whom the consent process for the SVI Study is initiated but randomization is not performed will be recorded on the SVI Screen Failure Log. A reason for exclusion for each of the patients will be recorded. Further details on the completion of the Screen Failure Log are located in the SVI Manual of Procedures (MoP).

7.0 SUBJECT CONSENT

7.1 Pre-Consent Eligibility Assessment

***Eligibility assessment will include**:*

1) Verification that all pre-procedural inclusion/exclusion criteria have been evaluated correctly;
2) Evaluation and documentation of relevant medical history;
3) Documentation of medication history;
4) Verification that all required information has been documented;
5) Signed and dated informed consent.

7.2 Presentation of Informed Consent

Consent will be obtained by either the Principal Investigator or by individuals approved by the Principal Investigator and whose names and copy of their curriculum vitae have been submitted to the SDMC. The initial consent will be the most recent IRB/REB-approved version. During the consent process the objectives of the study, as well as the risks and benefits of enrolling will be explained in detail to potential subjects.

Informed consent will be obtained from subjects in the pre-procedure preparation area at the time of obtaining ERCP consent, as part of normal patient care at the institution. The Informed Consent process will be documented in the subject record to include a review of the trial, the informed consent document, and that subject questions were answered prior to signature of the consent. Subjects will receive a copy of the signed and dated informed consent document and the original signed and dated consent form will be placed in the subject record. Original informed consent documents will be maintained on-file at each participating center. Once consented and enrolled into the trial, subjects will be issued a unique code to be used on data collection forms and other research records throughout the duration of the trial. Consent to procure outside medical records will also be obtained from study subjects in the event they are admitted to an outside facility after the ERCP.

To maximize recruitment, all patients without exclusion criteria will be asked to consent for the study, even if they do not meet any pre-procedural inclusion criteria. This strategy will increase enrollment because a subset of subjects will only become eligible for the study on the basis of meeting one or more intra-procedural inclusion criteria.

8.0 STUDY PROCEDURES

8.1 Screening/Baseline Visit

The following events will occur during the baseline screening visit, on the day of the procedure in the pre-ERCP preparation area or during a clinic visit preceding the ERCP.

8.1.1 Informed Consent

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

8.1.2 Medical History & Record Review

Study-relevant medical history will be reviewed and documented. This will include questions about past medical history, including the indication for ERCP, prior history of PEP, and recurrent pancreatitis.

8.2 Endoscopic Retrograde Cholangiopancreatography (ERCP)

8.2.1 Participating endoscopists

All study ERCPs will be performed or directly supervised by board certified gastroenterologists with specialized expertise in ERCP who are faculty physicians at participating study centers. A proportion of study cases will involve trainees at varying stages of ERCP proficiency. The extent of participation of the trainee in the study ERCP will be left to the discretion of the attending endoscopist, although the degree of trainee involvement in the case, including their involvement in the various components of the ERCP, will be formally collected.

8.2.2 ERCP & Follow Up

The activities and procedures that will occur during the ERCP, recovery period, and follow up are outlined, and each procedure described in detail below.

8.2.3 ERCP Procedure

- **Standard Medical Procedure Consent (Non-Research):** Subjects will review and sign a standard medical ERCP consent form (non-research) prior to the ERCP procedure.
- **Pre-Procedure Preparation:** Patients will have been advised to prepare for the ERCP prior to arrival, including instructions not to eat or drink anything after midnight the night before the procedure, or 6-8 hours prior, depending on the time of the procedure. All ALLERGIES should be reviewed and reported prior to ERCP. Patients are also advised what, if any, medications to avoid and/or medications that may require dosing or time changes (i.e., Metformin, insulin, anticoagulants). If approved by the physician, a small amount of liquid may be allowed to swallow important medications.
- **ERCP Procedure:** Almost all components of the ERCP and related interventions, except for prophylactic pancreatic stent placement, will be dictated by the performing endoscopist. The endoscopists will only use devices approved by the FDA or Health Canada during the ERCP.

8.2.4 Randomization

During the procedure, when one or more inclusion criteria have been met AND it has been determined that none of the exclusion criteria are present, AND the papilla (major or minor depending on indication) has been visualized and deemed accessible, the subject will be randomized to receive a 100 mg of rectal indomethacin (two 50mg suppositories) only or the combination of PSP and 100 mg of rectal indomethacin in a 1:1 fashion using a web-based electronic randomization system that will be accessed on a computer within the endoscopy suite. The randomization schedule will be generated centrally at the data coordinating center and will ensure treatment balance within site.

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

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

8.2.5 Indomethacin Administration

Indomethacin suppositories will be administered to subjects in both study groups by an endoscopy nurse, technician, or the endoscopist at the time of randomization during the ERCP. Rectal indomethacin was selected (as opposed to diclofenac) because it is approved by the FDA and Health Canada and commercially available in the United States and Canada. This dose of indomethacin is congruent with all prior studies evaluating rectal NSAIDs in PEP prevention, wherein a 100 mg dose of rectal NSAIDs is administered in the peri-procedural period. The rectal route was selected on the basis of available clinical data suggesting that only rectal NSAIDs are effective in PEP prophylaxis, perhaps due to more rapid and complete bioavailability. Several recent meta-analyses have confirmed the effectiveness of rectal NSAIDs for preventing post-ERCP pancreatitis, and existing practice guidelines recommend their use in all patients undergoing ERCP.

8.2.6 Pancreatic Stent Placement

Patients randomized to the PSP group will undergo stent placement at the appropriate time during the ERCP. The technique by which prophylactic pancreatic stents are placed and the type of stent used will not be directed by the study protocol but rather deferred to the judgment and expertise of the endoscopist. This approach is intended to mimic real-world practice, wherein variations in stent type, caliber, and length exist.[18] Specific information regarding stent make/model, caliber, length, guidewire used, amount of time required for deployment, and difficulty of stent placement will be collected to allow exploratory analyses of how stent characteristics influence PEP risk. For cases in which a pancreatic stent is placed to facilitate biliary access (precut sphincterotomy over a stent) or pancreatic sphincterotomy, if the subject is randomized to the indomethacin alone group, the pancreatic stent will be removed before the termination of the case.

8.2.7 Intra-Procedural Intravenous Fluid Administration

Intravenous fluid (IVF) administration during the ERCP will be left to the discretion of the clinicians involved in the ERCP (attending endoscopist, trainee, anesthesia personnel). Since IVF type and rate may influence the development of the primary and secondary endpoints, all decisions regarding IVF administration made by the endoscopy team must be implemented prior to randomization. After randomization, unblinded study personnel should not recommend any changes in IVF administration. For example, an attending endoscopist may ask anesthesia personnel to increase the IVF rate once he/she determines that the case has become high risk due

to a difficult cannulation. However, no further changes can be recommended or made once randomization has occurred.

After randomization, urgent changes in IVF administration in response to hemodynamic instability or volume overload will be dictated by anesthesia personnel. All efforts should be made to ensure that these anesthesia personnel are not aware of the overall purpose of the study nor are they fully aware of study group assignment.

Specific information regarding IVF administration immediately before, during, and after the case will be collected in the CRF to allow exploratory analyses of how IVFs influence PEP risk.

8.2.8 Maintenance of the Blind

Since the endoscopist(s), endoscopy nurse, and technician/assistant involved in the ERCP will be aware of whether or not a stent was placed, these individuals **will not** be involved in the subsequent post-procedure care of the patient until at least 48 hours after the procedure, at which point the presence or absence of the primary endpoint (PEP) will have become apparent. This approach is critical to maintaining blinding (of patients, treating clinical personnel, and outcome assessors), which ensures equal co-interventions between study groups and unbiased adjudication of the primary outcome.

In order to ensure blinding of 1) subjects, 2) healthcare providers making clinical decisions that may directly impact the primary endpoint (e.g. rate of intravenous fluid administration, amount of analgesics delivered, decision to keep the patient in the hospital a second night), and 3) those who will adjudicate the study outcomes, the endoscopy report and medical record will NOT state whether a stent was placed. Instead, the following statement will be input into the endoscopy report:

> *"This patient was enrolled in study protocol #xxxxxx in which he/she was randomized to receive either a dose of indomethacin only **or** both indomethacin and a prophylactic pancreatic stent for the prevention of post-ERCP pancreatitis. If this patient received indomethacin and a stent, he/she will be contacted 1-4 weeks after the ERCP to arrange an abdominal XRAY that is necessary to ensure spontaneous passage of the pancreatic stent."*

If a stent was indeed placed, 1-4 weeks after the procedure, the endoscopist or their clinical support personnel will contact the subject and deliver a requisition for an abdominal XRAY. Ensuring that the XRAY is performed, following up on the results, and removing retained stents will be the responsibility of the treating endoscopist and his/her support staff, as per standard clinical protocols. Patients who receive this requisition will be unblinded to study group assignment although this will occur after the primary endpoint has been established. This unblinding could theoretically impact development or assessment of the secondary endpoint, although subjects will be **discouraged from mentioning** their randomization assignment to study personnel during the 30-day telephone visit.

We realize that a small fraction of study subjects will undergo abdominal imaging within the first 2 post-ERCP days, the results of which may provide the clinical care team with information pertaining to PSP. This is an unavoidable threat to blinding; however, we believe that this will occur in only a small percentage of enrolled subjects.

8.3 Follow-Up Assessments

8.3.1 Immediate Post-Procedure Care, Observation, and Discharge

Subjects will be observed in the recovery area for as long as clinically appropriate after the termination of the procedure. To ensure that the unblinded endoscopist does not influence the care of a study subject, each participating endoscopist will have the option of implementing a provider-specific post-procedure order set that is **activated prior to randomization** and executed uniformly regardless of a subject's study group assignment. This order set may include intravenous fluid, analgesic, and antiemetic administration as well as parameters for hospital admission. If activated, all clinical decisions pertaining to the immediate post-procedure care of the subject and to hospital admission will be dictated primarily by this order set. If an order set is not available or has not been activated, the endoscopist will be responsible for designating a **blinded** clinician who will oversee the post-procedure care of the patient. In these cases, all post-procedure clinical decisions (including IVF and analgesic administration & the decision to admit to the hospital) will be dictated by this blinded healthcare provider. Once a patient is admitted, all clinical decisions will be made by an inpatient team that **cannot include the endoscopist** for at least 48 hours after the ERCP.

Performing endoscopists are permitted to communicate with patients and their families/friends after the procedure as long as they do not provide any direct or indirect information about treatment group assignment.

Performing endoscopists may ask that subjects be admitted to the hospital for observation or for additional post-procedure care depending on factors that occurred during the case which are unrelated to the study group assignment.

8.3.2 Post-Intervention Evaluations

A study coordinator will perform two follow-up contacts:

1) *3*-5 days after the ERCP and,

2) 30 days after the ERCP.

The goal of the first follow-up is to ascertain those data necessary to adjudicate the primary endpoint. The goal of the second follow-up is to ascertain those data necessary to adjudicate the secondary outcome and assess for delayed serious adverse events. Permission to procure outside medical records (in the event a subject is admitted to a non-study center) will have been obtained at the time of consent.

Visit Windows*:* The timeline of the assessments is based on a start date of randomization. Although every attempt should be made to contact the subject at these pre-specified intervals, it is possible that the assessments may occur within a window around the intervals. The study data should always be collected regardless of its tardiness, however preferable windows are 3-5 days after ERCP for the first assessment, and 30 days +/- 5 days for the second assessment.

Subjects' medical records may be reviewed for up to 5 years after enrollment to review ERCP results, additional ERCP findings, hospitalizations, and laboratory or radiology data. Study samples (see below) and clinical data will be stored indefinitely as long as consent has not been withdrawn.

8.4 Biorepository

To improve our understanding of the mechanisms by which indomethacin protects against PEP, as well as to further explore the incompletely understood pathophysiology of PEP, we will establish a repository of whole blood, serum, plasma, urine, duodenal fluid, and stool specimens obtained from trial subjects on which future translational studies can be conducted.

Biologic specimens will be obtained from the first 1430 study subjects (original sample size) who agree to donate their samples. Subsequently, collection of specimens will be optional and dependent on a combination of individual site resources and subject consent. Specimen storage and tracking will be handled by the Clinical Ligand Assay Service Satellite (CLASS) Biosample Repository at the University of Michigan. The CLASS repository is a professionally managed biosample repository described in more detail in the "Resources and Environment" section and at: http://swan.class.sph.umich.edu/html/fn_classovr.htm. The samples will then be transferred in increments to the NIDDK Central Repository for long term storage.

Complete procedures for sample procurement, processing, labeling, storage, tracking, and sharing are detailed in the current version of the MoP available on WebDCU™.

8.5 ERCP Skills

An assessment of endoscopic skill and correlation with ERCP outcomes may be performed in a subset of subjects enrolled in SVI. The endoscopic and fluoroscopic footage of ERCP procedures in SVI subjects may be recorded. Participating endoscopists will each submit 5-20 videos of themselves performing complete ERCP procedures. The endoscopists will be asked to submit consecutive SVI cases, with at least 3 cases in which a biliary and/or pancreatic sphincterotomy is performed. After quality assurance of the footage and removal of all identifiers and non-critical footage, each video will be distributed to other endoscopists for peer rating. The correlation between endoscopic skill and adverse events will be examined to more concretely understand this relationship and to elucidate the composition of a skillful ERCP.

9.0 PROCEDURE FOR UNBLINDING

The medical safety monitor, clinical personnel treating the patient for the first 48 hours after ERCP, subject, and outcomes adjudicators are blinded to treatment assignment. Every effort should be made not to break the blind.

In the event of either an accidental or deliberate unblinding event, the clinical site individual who was unblinded must report the incident within one (1) calendar day of the unblinding in WebDCU™. The incident should not be discussed with other clinical site personnel.

In those cases of an emergency where the medical management of the subject would change based on the study procedure, emergency unblinding is authorized. Refer to the SVI MoP for emergency unblinding procedures.

10.0 DISCONTINUATION OF PARTICIPATION

10.1 Subject Withdrawal

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

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

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

10.2 Subject Removal from Study

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

(1) Significant protocol violation, either on the part of the subject or Investigator.

(2) Refusal of the subject and/or the legal guardian to remain in the study (i.e. consent withdrawal).

(3) If the physician or the Medical Safety Monitor believes it is in the subject's best interest to discontinue participation in the study.

(4) Administrative reasons, e.g., MUSC or NIDDK termination of the study.

10.3 Procedure for Discontinuation

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

(1) Adverse event assessment.

(2) Attempt to perform final follow-up evaluations.

(3) Complete the End-of-Study form, including an explanation of why the subject is withdrawing or withdrawn.

10.4 Subject Lost to Follow-Up

All attempts to make contact with the subject will be documented in the study database. A plan of action for following up on subjects who cannot be contacted via telephone is outlined in the SVI Manual of Procedures. When all possible attempts to locate the subject have failed, that subject will be considered ‘lost to follow up’.

10.5 Re-Entering the Study

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

10.6 Subject Transfers

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

11.0 OUTCOMES DEFINITIONS

11.1 Primary

The primary endpoint is post-ERCP pancreatitis, based on consensus (Atlanta) guidelines:[19] 1) New or increased pain in the upper abdomen **and** 2) amylase or lipase ≥ 3x the upper limit of normal 24 hours after the procedure **and** 3) hospitalization (or prolongation of existing hospitalization) for at least 2 days (at least the night of ERCP & following night).

Using these consensus guidelines as a diagnostic framework, three adjudicators will independently assess for the development of PEP based on review of a site-provided AE narrative and medical records for each study subject ***hospitalized within 2 days after the ERCP.*** The primary outcome will be adjudicated by an independent committee consisting of the MSM and two other voting members. To help the adjudicators assess post-procedure pain, the AE narrative and the pre and post-ERCP numeric pain scale results administered by the study coordinator will be available to the adjudicators. PEP will be declared if 2 of the 3 adjudicators determine that a subject has experienced post-ERCP pancreatitis. This committee-adjudicated outcome will be used for the primary analysis. Complete details of the outcomes adjudication process are available in the MoP.

11.2 Secondary

The secondary endpoint is moderate-severe post-ERCP pancreatitis, also defined on the basis of consensus guidelines: mild PEP is defined as pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for ≤3 days. Moderate PEP – pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for 4-10 days. Severe PEP – pancreatitis that results in hospitalization (or prolongation of existing hospitalization) for > 10 days, or leads to the development of a pancreatic fluid collection, or requires additional endoscopic, percutaneous, or surgical intervention. This outcome will also be adjudicated by the independent panel. Subjects may be unblinded to study group assignment after 7 days (if they receive notification for pancreatic stent follow-up), and thus the study is only partly double-blinded for the secondary endpoint.

12.0 DATA COLLECTION, MANAGEMENT, AND QUALITY CONTROL PROCEDURES

Comprehensive data coordinating functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the data and safety monitoring board (DSMB) will be provided by the SDMC at MUSC.

12.1 Data Management

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

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

Upon entry of CRFs into the study database, quality control procedures will be applied at each stage of data handling in order to ensure compliance with GCP guidelines, integrity of the study data, and document processing system reliability.

All sites will be monitored by the SDMC and site monitors will conduct periodic site visits to review source documents and case report form information. A quality assurance record audit will be implemented. Audit findings will be used to identify and correct problems.

12.2 Site Monitoring

The SVI Site Monitoring Plan will be guided by the FDA Guidance on Risk-Based Monitoring and will be a combination of remote and on-site monitoring. Briefly, the designated monitor(s) will be able to check regulatory documents and certain CRFs remotely and the SDMC will work with each site to develop the best plan (i.e., remote access to medical records or uploading files to WebDCU). In addition to remote monitoring, the monitor(s) will visit the Clinical Centers at specified intervals for the purposes of comparing source documents (such as hospital/clinical charts) to electronic Case Report Forms (CRFs) and database verification. This review will also verify adherence to local regulations for conducting clinical research, protocol eligibility criteria and protocol schedule, and to ensure the consistency, accuracy, and completeness of the data. At all times the monitor will ensure that subject confidentiality is maintained. The investigator agrees that he/she will ensure that any issues, problems, or need for corrections that arise during the conduct of the study will be resolved in a timely manner. Additional details are located in the current version of the SVI Manual of Procedures located in WebDCU™.

12.3 Data Security and Confidentiality

During the course of the trial, user access to the files with subject identifiers, treatment assignment and files with study outcomes will be restricted to core SDMC staff with any exceptions to be approved by the Executive Committee.

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

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

13.0 STATISTICAL CONSIDERATIONS

13.1 Non-Inferiority Margin

Given the high economic and opportunity costs associated with pancreatic stent placement, as well as the risks of attempted but unsuccessful insertion, we believe that rectal indomethacin would replace PSP in clinical practice if we can demonstrate that it results in less than a 5% greater PEP rate compared to the combination of indomethacin and PSP. The 5% threshold is referred to as the non-inferiority margin.

The value of this margin is based on a combination of statistical reasoning and clinical judgment and was chosen to ensure that the overall PEP proportion of the new treatment (indomethacin

alone) demonstrates a clinically *unimportant* difference from the active comparator arm (the combination of stent and indomethacin) as well as a clinically relevant superiority over a putative placebo (i.e., stent alone).

From a statistical perspective, the margin should retain at least 50% of the superiority of the combination of stent and indomethacin (the active control in the trial) when compared to stent alone.[20,21] Our recent indomethacin RCT conducted in high-risk patients revealed that the absolute risk difference in the proportion of subjects with post-ERCP pancreatitis between those that received indomethacin plus stent versus those who received stent alone was 6.4% (95%CI: 0.5%, 12.3%) (27). Therefore, taking a fraction of this value gives a non-inferiority margin (δ) of 3.2% (δ = .5*6.4).

Independent to the statistical approach, a questionnaire was circulated to clinical stakeholders regarding how much better (in absolute terms) combination therapy would have to be in preventing PEP as compared to indomethacin alone to justify continuing the use of combination therapy in clinical practice. Seven of 11 respondents said that combination therapy would have to be 10% more effective and the remaining 4 said that it had to be at least 5% more effective.

Based on both the statistical and clinical information, the pre-specified non-inferiority margin was set at 5%. The clinical investigators unanimously judged that a difference in treatment effect of 5% or greater constitutes an important difference between PEP proportions between the two treatment arms indicating that a strategy of indomethacin alone is inappropriate to adopt due to the higher risk of PEP. Although the statistical guidance suggested a lower margin (3.2%), a non-inferiority margin of 3.2% was considered impractical as it would require a sample size of approximately 1700 subjects per arm (to maintain the proposed 85% power), and it was strongly perceived by experts in the field that a margin of 5% would be adequate to definitively impact clinical practice if non-inferiority is declared.

13.2 Sample Size Calculation

The sample size is estimated using a confidence interval approach focusing on the upper confidence limit for a difference in proportions via simulation using nQuery.[23] Based on results of our prior randomized controlled trial, the rate of PEP in subjects receiving the combination of indomethacin and PSP is estimated to be 9.5% for the risk-adjusted population and 9.7% of the unadjusted population.[22] We chose to use the higher (unadjusted) proportion for a more conservative approach to sample size estimation. Based on this information, the study is powered to assure 85% likelihood of identifying less than a 5% absolute difference (non-inferiority margin) in PEP rates between the two treatment groups. For sample size estimation for a non-inferiority design, we set the independent proportions to be equal between the two treatment arms, the confidence level for the upper limit at 0.975 (equivalent to a one-sided 2.5% level test) and the upper limit of the confidence interval at 5% (NI margin). The maximum sample size required for randomization is 1300 subjects (650 per treatment group). Due to the potential non-adherence rate, the total sample size is inflated by 5% to account for a small probability of treatment crossovers or losses to follow-up. Thus, a total of 1430 subjects will need to be enrolled and randomized. The sample size was increased to a maximum of 2,180 in order to attain 85% power. This increase was due to the DSMB recommendation based on the review of the planned blinded sample size re-estimation in September 2017.

We recognize that sample size estimation is based on assumptions and if the control (i.e., combination arm) PEP rate is higher than 9.7% then we may begin to see a decrease in power. To reduce the likelihood of an underpowered study due to incorrect sample size assumptions, a blinded sample size re-estimation will be conducted at the time of the first planned futility analysis (but prior to the futility analysis). The study Statistical Analysis Plan (SAP) contains the details of this process.

13.3 Statistical Analyses

An intention-to-treat approach will be the primary basis for analysis. For the analysis of the primary and secondary endpoints, the two-sided 95% upper confidence bound (equivalent to the one-sided 97.5% upper confidence bound) of the observed risk difference in the proportion of patients developing post-ERCP pancreatitis (or moderate-severe PEP) between the two treatment groups (indomethacin alone – combination of indomethacin and PSP) will be calculated. Indomethacin alone will be declared non-inferior to combination therapy if the two-sided 95% upper confidence bound of the treatment difference is less than 5%. If indomethacin is found to be non-inferior, an analysis for superiority will be conducted using a one-sided two sample test for independent binomial proportions.[24]

Exploratory subgroup analyses will be performed as specified in the Statistical Analysis Plan (SAP). These exploratory subgroup analyses will allow the development of hypotheses about subgroups of patients that may particularly benefit from PSP.

All statistical analyses are outlined in the study Statistical Analysis Plan.

13.4 Interim Analysis

Two interim analyses for futility using conditional power will be conducted when approximately one-third (N~472) of the original sample size and one-half (N~1090) of the revised sample size (N=2180) have been evaluated for the primary outcome and all of the outcomes to be used in the analysis are adjudicated. The goal of the interim analysis plan is to determine whether to stop the trial early because it is unlikely to show non-inferiority at the final analysis. A conditional power will be calculated to assess the probability of observing non-inferiority at the final analysis conditional on the observed data and assumptions on the PEP event rates for the remainder of the trial. Conditional power will be calculated under two different assumptions: 1) the assumption that the PEP rates in the two treatment arms for the remainder of the trial will be the same as those hypothesized (pC=9.7%; pI=9.7%); and, 2) the assumption that the PEP rates observed at the interim analysis will be maintained for the remainder of the trial. See the Statistical Analysis Plan for more details.

13.5 Data and Safety Monitoring Plan (DSMP)

Our previous large-scale RCT suggested that indomethacin alone may be more effective (safer) than any strategy involving PSP because it avoids manipulation of the pancreatic orifice and instrumentation of the pancreatic duct, interventions that are necessary to place a pancreatic stent but are known to contribute to pancreatitis.[16] Nevertheless, PSP is routinely used in clinical practice for the prevention of PEP in high-risk cases. Our proposed comparative effectiveness study will randomize 50% of subjects to ***not*** receive a pancreatic stent even though one would likely have been placed in routine clinical practice. We are therefore ethically obligated to ensure

that withholding this intervention from high-risk patients as part of this study protocol is not causing excess harm.

Study data and safety will be monitored by the NIDDK-appointed Data and Safety Monitoring Board (DSMB). This board serves in a consultative capacity to inform the NIDDK decisions regarding conduct of the study.

The complete DSMP is presented in a separate safety monitoring plan document. In brief, there will be an independent medical safety monitor (MSM) who reviews in real-time all submitted serious adverse events and receives quarterly safety reports from the SDMC. The MSM will provide his/her review of the relevant SAEs regarding seriousness, relatedness and expectedness. Both the site and MSM entries will be presented to the DSMB.

14.0 REGULATORY AND ETHICAL OBLIGATIONS

14.1 Informed Consent

In accordance with US FDA regulations (21 CFR 50) and guidelines (Federal Register, May 9, 1997, Vol. 62, Number 90–ICH Good Clinical Practice Consolidated Guideline), it is the investigator's responsibility to ensure that legally effective informed consent is obtained from the participant before participating in an investigational study, after an adequate explanation of the purpose, methods, risks, potential benefits and participant responsibilities of the study. Procedures that are to be performed as part of the practice of medicine and which would be performed whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for research.

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

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

14.2 Institutional Review Board/Research Ethics Board

In accordance with US FDA (21 CFR 56) and Health Canada regulations and guidelines (US Federal Register, May 9, 1997 Vol. 62 Number 90 - ICH Good Clinical Practice Consolidated Guideline), all research involving human subjects and changes to the research plan must be reviewed and approved by a local IRB/REB.

14.2.1 Initial Review and Approval

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

14.2.2 Amendments

Protocol amendments may only be made with the prior approval of the SVI Executive Committee and the NIDDK. Substantive changes to the protocol require DSMB review prior to implementation. The Principal Investigator must agree to, and obtain approval from the IRB/REB for, all protocol amendments and revisions to the informed consent document as dictated by Executive Committee. The Principal Investigator at each clinical center must obtain approval from the IRB/REB for all revisions to the informed consent document, whether initiated by the investigator or Executive Committee.

14.2.3 Annual Renewal

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

14.2.4 Pre-Study Documentation Requirements

The Principal Investigator at each Clinical Center is responsible for uploading all required regulatory documents to the WebDCU™ for review by the SVI Project Manager or SDMC prior to recruitment.

14.3 Subject Confidentiality

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

15.0 ADMINISTRATIVE AND LEGAL OBLIGATIONS

15.1 Study Termination

The study will be complete when all subjects have had their final study assessments. The sponsor or Executive Committee reserves the right to terminate the study if new information becomes available on the safety or efficacy of the study product or if such action is justified.

If the Executive Committee terminates the study or individual study sites for the reasons given above, the investigator will provide any outstanding data or documentation (e.g., case report form pages) considered appropriate by the Coordinating Center at the time.

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

16.0 ORGANIZATIONAL INFRASTRUCTURE

16.1 Executive Committee

The Executive Committee (EC) is composed of the study PI, the SDMC PI, the project manager, the NIDDK program officer, and the NIDDK project scientists.

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

Throughout the study, the Executive Committee will meet monthly and *ad hoc* as needed. The Executive Committee will coordinate Investigator Meetings and/or continued training & education. Additional details including membership information are located in the current version of the SVI Manual of Procedures located on WebDCU™.

16.2 Steering Committee

The Steering committee (SC) is composed of the study PI, site PIs, SDMC PI, and the NIDDK project scientist.

The SC has overall responsibility for assuring the scientific, clinical and ethical integrity of the study. The SC will meet on a regular basis, at least four times annually and in between as circumstances indicate. This committee's comprehensive list of duties/responsibilities is detailed in the current version of the SVI Manual of Procedures located on WebDCU™.

16.3 Standing Committees

Potential standing committees will be convened to address key study issues, such as the biorepository, ancillary studies, and publications. Further details regarding the standing committees can be found in Manual of Procedures located on WebDCU™.

16.4 Statistical and Data Management Center

The Statistical and Data Management Center (SDMC) is housed in the Department of Public Health Sciences Data Coordination Unit (DCU) at MUSC. Dr. Valerie Durkalski will assume overall responsibility of the SDMC (see budget justification). The SDMC will be responsible for the data management and analysis for the Trial. Specifically, they will: (1) develop the case report forms; (2) create and maintain the study database, including extensive error checking and subject registration/randomization; (3) develop and maintain a Data Management Plan; (4) assure data security and appropriate archiving of data files; (5) provide statistical support for the trial and produce interim and final reports to the Executive Committee and the DSMB; and (6) assist with the closeout of the Trial, including data transfers. The MUSC DCU, which will house the SDMC, has extensive experience with all aspects of data management for multicenter clinical trials, and is in full compliance with the Good Clinical Practice (GCP) guidelines and regulations for conducting clinical trials. All systems used in the management and storage of clinical trial data are maintained on site at the offices of DCU (refer to DCU Resource Page). The SDMC's experience as a coordinating center for multicenter clinical studies of similar type has enabled the group to develop processes that minimize the burden on the site research personnel, and allow for an optimal

combination of technology and resources to ensure all aspects of the project are handled effectively and efficiently.

16.5 Medical Safety Monitor

The Medical Safety Monitor (MSM) is a licensed physician with relevant expertise who is independent of the research study. The independent MSM responsibilities include: on-going review and familiarity with the SVI protocol; review of periodic cumulative safety monitoring reports to ensure the protocol is conducted safely and according to GCP and regulatory requirements; review of individual serious adverse event reports immediately after they are reported and on-going feedback regarding safety throughout the SVI study.

16.6 Data and Safety Monitoring Board

The monitoring of data quality and subject safety in this trial will be overseen by an appointed Data and Safety Monitoring Board (DSMB). The DSMB members are appointed by the NIDDK. The members will have a meeting with the PI and study statistician prior to study commencement to discuss the protocol as well as content and format of DSMB reports. The SDMC will prepare the requested reports at the pre-specified time intervals. Both open and closed reports will be distributed – open reports will be available to the Executive Committee members and will be blinded to treatment assignment while closed reports will only be available to the DSMB members and will only be unblinded upon request by the DSMB members.

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